NOVARTIS

Clinical Development

LDK378/Ceritinib/Zykadia

LDK378X2103 / NCT01742286

A phase 1, open-label, dose-escalation study of LDK378 in pediatric patients with malignancies that have a genetic alteration in anaplastic lymphoma kinase (ALK)

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous final version of SAP

Version	Date	Changes
1.0	07-MAR-2016	Initial Version
Amendment 1	17-OCT-2016	Front page: • Author changed. [redacted] is the new trial statistician. Section 2.1 • The description of cohort was updated to reflect the expanded cohort. • Definition of end of study was updated. Section 2.2 • Rules for treatment classification for FAS was added. Table 2-1 was included to illustrate the treatment regimen groups. • Method to calculate the actual dose level was clarified. Classification rules for safety set was updated per protocol terms. • Definition of evaluable trough PK concentration was updated. Section 2.4 • Prior antineoplastic therapy surgery was updated to exclude diagnostic biopsies. • List of prohibited concomitant medications was added as Table 2.2. Section 2.6 • Criteria for determination of BOR per RECIST 1.1 were updated. Section 2.10 • Reported primary and secondary PK parameters were updated. Table 2-6 was also updated accordingly. • PK summaries by age groups was moved from "LDK378 concentrations" to "LDK378 PK parameters". • Dose proportionality (DP) analysis was updated to clarify which measures are applicable. Section 4 • Table 4-1 was added to summarize changes to protocol specified analysis or descriptions and rationale

		Section 5.3 • calculations of dose interruptions and dose changes were clarified Section 5.6 • Definition of last contact date was added.
Amendment 2	30-May-2019	Front page: • Author changed. [redacted] is the new trial statistician. [redacted] List of abbreviations: • Some of the abbreviations were added to the list Section 1 • Updated the version of protocol used in this SAP amendment Section 1.1 • Updated the language to clarify the two parts of this study Section 2.1 • Updated the text for data analysis general information. • Updated the text to clarify that analysis and CSR will be prepared at the end of the study. • Updated the definition of end of study • Updated the labels for expansion group • Updated the age cut-off used in subgroup analysis from 5 years to 7 years • Updated the text to refer to 5.5.2 for further details Section 2.2 • Updated the text for the safety set with an example to define dosing groups • Updated the specifications for the Dose determining set to be in the escalation phase only • Updated the text for an evaluable trough PK concentration Section 2.3 • Updated the cut-off for subgroup analysis from 5 years to 7 years • Updated the text to detail the diagnosis of RECIST and Lymphoma separately • Added abbreviations for SOC and PT

- Updated the section of Prior antineoplastic therapy
- Updated the text for screen failures

Section 2.4

- Updated the specifications for dose exposure and intensity
- Removed prior antineoplastic therapy to baseline section and updated specifications for concomitant therapy
- Deleted table 2.2

Section 2.5

- Updated the specifications to specify the MTD/RDE
- Updated the specifications for DLT outputs

Section 2.6

- Updated the text for ORR.
- Updated the specifications for MIBG response score output
- Updated the specifications for BOR per RECIST 1.1 and IWG criteria
- Updated the specifications for Duration of response and time points

Section 2.7

- Updated the specifications for PFS

Section 2.8

- Updated the text for safety analyses
- Updated the specifications for AE summaries
- Updated the source for AESI definition
- Updated the text for lab data
- Updated the text for ECG
- Updated the specifications for Vital Signs

Section 2.10

- Updated the PK parameters
- Updated table Noncompartmental pharmacokinetic parameters
- Updated the specifications for Ctrough and average Ctrough

Section 5.2

- Updated the table for patient classification rules

Section 5.3

- Updated the text for dose interruptions and dose changes

Section 5.4

- Updated the text for Implementation of RECIST and Cheson guidelines

Section 5.6

- Updated the text for missing date handling
- Updated the text for conmeds date imputation
- Updated the text for incomplete assessment dates for tumor assessment
- Updated the specifications for incomplete date for death
- Updated the speicifications for last contact date
- Updated the specifications for incomplete dates for last dose of study drug
- Updated the language for incomplete dates for disease progression prior to start of study drug

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List of abbreviations

AE	Adverse event
ALCL	Anaplastic large cell lymphoma
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
AUCtau	Area under the plasma (serum, or blood) concentration versus time curve from time zero to end of dosing period
bid	bis in diem/twice a day
CSR	Clinical Study report
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
eCRF	Electronic Case Report Form
IMT	Inflammatory myofibroblastic tumor
IVR	Interactive Voice Response
IWR	Interactive Web Response
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NCI	National Cancer Institute
o.d.	Once Daily
OS	Overall Survival
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
T1/2	Half-life
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The statistical plan (SAP) describes the planned statistical methodology for the analysis of the data from study CLDK378X2103, 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).

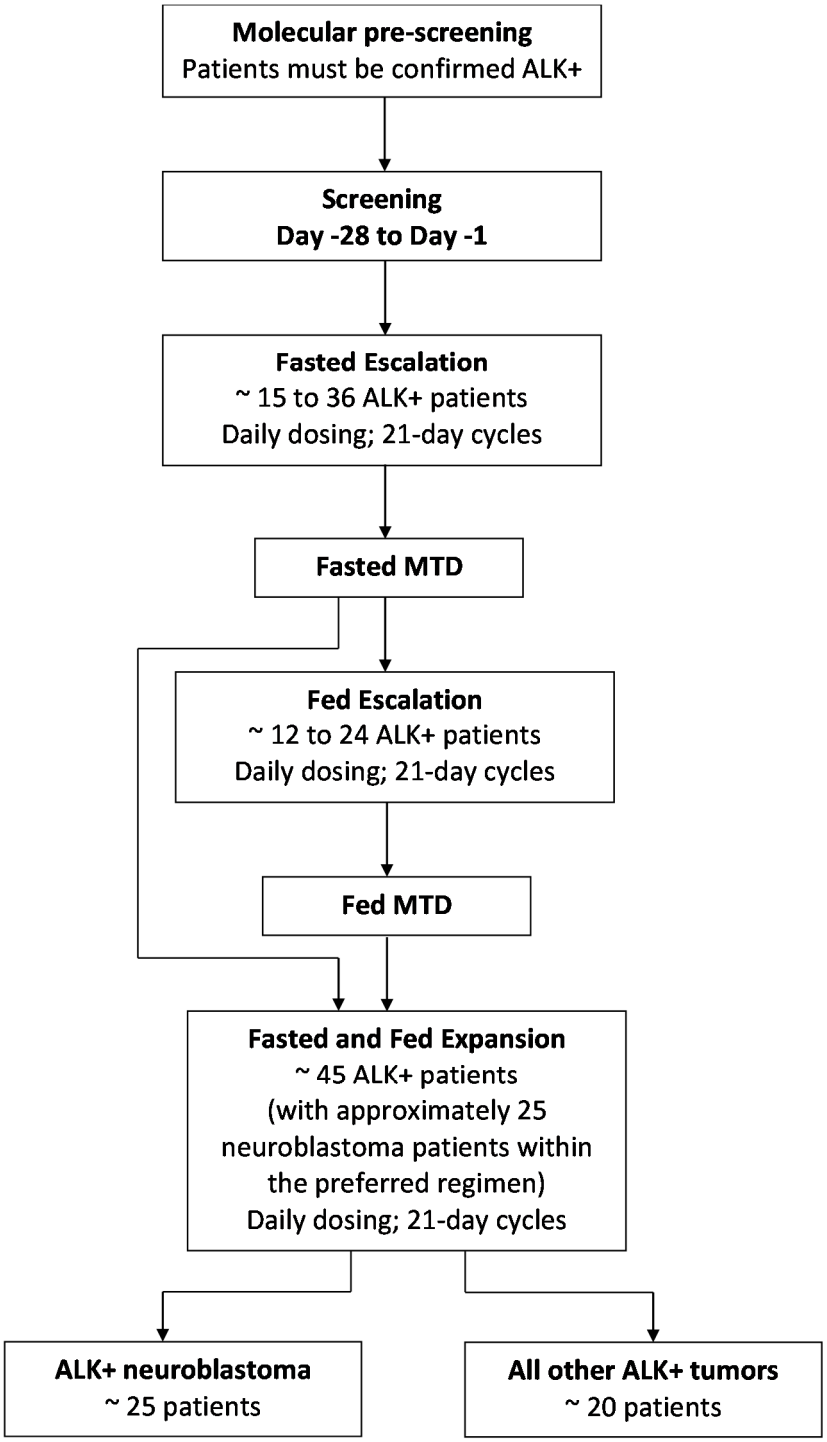
The content of this SAP is based on protocol CLDK378X2103 Amendment 8. All decisions regarding final analysis, as defined in the SAP document, have been made prior to database lock of the study data.

1.1 Study design

This is a multi-center, phase I, open-label, dose escalation study to determine the maximum tolerated dose (MTD) and/or the recommended dose for expansion (RDE) of ceritinib administered orally on a continuous daily dosing in both fasted (drug should be taken at least 2 hrs after the last meal and patient should not eat until 1 hr after drug is taken) and fed (drug should be taken within 30 minutes after finishing a low-fat light snack containing 100-300 calories and 1.5-2 grams of fat) pediatric patients with an advanced malignancy carrying a genetic alteration of ALK that has progressed following standard therapy, or for which no standard therapy exists.

The study has two parts, one that includes a dose escalation part performed in the fasted and fed states, and an expansion part performed at the MTD or RDE on the fasted regimen and on the fed regimen separately in order to better evaluate safety, tolerability, and preliminary evidence of antitumor activity in 2 groups of patients, one restricted to patients with ALK-activated neuroblastoma and the second including all other ALK-activated tumors. 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). 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).

Figure 1-1 Overview of study design



Dose-Escalation Phase

The primary objective of the dose escalation phase is to determine the MTD(s) and RDE(s) in both fasted and fed states.
In the fasted dose-escalation, approximately 15 to 36 patients will be enrolled. Successive cohorts of patients will receive specified doses of LDK378 until the MTD on fasted regimen is determined. Each cohort will consist of 3 to 6 newly enrolled patients. The first cohort will be treated with the starting dose of 300 mg/m^2.

A two-parameter Bayesian logistic regression model (BLRM) employing the dose-escalation with overdose control (EWOC) principle (Babb 1998, Neuenschwander 2008) will be used during the fasted dose-escalation for dose level selection and for determination of the MTD on fasted regimen.

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 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. It is anticipated that approximately 12-24 patients will be treated during the fed dose escalation.The same 2-parameter form of the BLRM will be used to estimate the dose-DLT relationships separately for fed patients. Data from fasted patients will be utilized to formulate a prior distribution for the BLRM parameters for fed patients. Details of the statistical model can be found in Section 14.1.3 of protocol.

Both fasted and fed dose escalation will continue until identification of the corresponding 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 planned dose (initially assigned dose level (mg/m2) on Cycle 1 Day 1).
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
    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.

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). 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.

Expansion Phase

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 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.

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. Additionally, analysis to determine the fed dose selected for the expansion phase is also dependent on the observed data.

1.2 Study objectives and endpoints

The primary objective of the study is to 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.

Table 1-1 Objectives and related endpoints

Objective	Endpoint
Primary	
Estimate the MTD and/or RDE of LDK378 as a single agent when administered orally to fed and fasted pediatric patients with ALK-activated tumors for fasted and fed regimens	Incidence rate of Dose Limiting Toxicities (DLT) during the first cycle of LDK378 treatment.
Secondary	

Objective	Endpoint
(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]

Abbreviations: area under the concentration-time curve (AUC) from time zero to the last measurable concentration sampling time, AUCtau, Area under the plasma (serum, or blood) concentration versus time curve from time zero to end of dosing period, Cmax, maximum concentration, Cmin, minimum concentration, MIBG, metaiodobenzylguanidine, Racc, accumulation ratio, T1/2acc, effective half-life calculated from Racc, Tmax, time to reach maximum plasma concentration. [redacted]

2 Statistical methods

This section and its subsections will be imported to section 9.7 of the CSR after the analyses have been conducted. This section of the SAP follows the CSR template structure of Section 9.7 as of the release date of this document. The text will be changed to past tense when imported into the CSR; references to sections of the SAP where additional details are provided for programming implementation may be removed in the CSR.

In what follows, study drug refers to LDK378 (certinib).

2.1 Data analysis general information

Data will be analyzed by Novartis Oncology Biostatistics and Statistical Programming personnel according to the data analysis section 10 of the LDK378X2103 protocol, which will be available in Appendix 16.1.1 of the Clinical Study Report (CSR). Important information is

given in the following sections and details are provided, from which Appendix 16.1.9 of the CSR will be written.

The data will be analyzed using SAS version 9.4 or later, and for Bayesian modeling, R version 2.13.2 or later, and WinBUGS version 1.4.3 or later. The Bayesian modeling of the dose-toxicity relationship used for dose escalation decision making and inference for the MTD is performed using internal Novartis R library functions (OncoBayes) created by Novartis's Methodology group and are run using R version 2.13.2 or later in the MODESIM/GPSII environment.

Data from patients who signed study informed consent in centers that participate in this study will be used in the analysis; due to expected small size of enrollment at individual centers, no center effect will be assessed. Each analysis will use all data in the database up to the analysis cutoff date, determined prior to database lock. Data collected after patients' withdrawal of informed consent for further participation in the study will not be reported (except for death date which might be obtained from public records).

Final CSR

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

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.

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.

General presentation of descriptive summaries

Qualitative data (e.g. gender, race) will be summarized by frequency counts and percentages. Percentages will be calculated using the number of patients in the relevant population or subgroup, as the denominator.

Continuous data (e.g. age, body weight) will be summarized by appropriate descriptive statistics (i.e. mean, standard deviation, median, minimum, and maximum).

Summary statistics for PK concentrations and PK parameters will include the following, unless otherwise specified: n, mean, SD, CV% mean, geometric mean, CV% of geometric mean, median, minimum and maximum.

Data from patients enrolled during the expansion phase in the applicable disease group at the MTD/RDE will be pooled with data from patients enrolled in the dose-escalation phase, unless otherwise specified (e.g. primary analysis of dose-DLT relationship).

Unless otherwise specified, analysis of efficacy data will be presented:

- by treatment group : A treatment group is defined by both dose level and regimen (fasted or fed). Data from patients in the expansion and escalation parts in the same treatment group will be combined.
- by expansion group: for patients in the pooled LDK378 MTD/RDE group
  - patients with ALK-activated neuroblastoma,
  - patients with ALK-activated IMT.
  - patients with ALK-activated ALCL.
  - patients with all other ALK-activated tumors.

The efficacy data of patients with lymphoma evaluated by IWG (Cheson) response criteria will be summarized/listed separately from the efficacy data evaluated by RECIST 1.1.

Unless otherwise specified, all summaries of PK data will be presented by treatment group and by expansion group as defined above.

All listings will be displayed by indication, treatment group, and patient, unless otherwise specified.

For safety, PK and all other summaries, data will be presented by treatment group unless otherwise specified.

The safety summary tables will include only assessments collected during the on-treatment period unless otherwise specified. For select items, shift tables or change from baseline summaries generated for laboratory, ECG, and vital signs may use data from pre-treatment period for baseline calculations. See Section 2.1.1 for key definitions of terms used in this SAP.

All data, regardless of observation period, will be listed and assessments collected in the pre-treatment or post-treatment period will be flagged in all the listings.

Subgroup analyses

If the number of patients allows (larger than or equal to 10), in addition to the population subgroups described above, efficacy endpoints (ORR) and adverse events (AEs) will also be summarized for patients in the LDK378 MTD/RDE group by the following subgroups:

- age (1 year to <7 years, 7 years to <12 years, 12 years to <18 years)

2.1.1 General definitions

Study drug and study treatment

Study drug and study treatment both refer to the Novartis investigational drug, LDK378 (ceritinib) and will be used interchangeably. LDK378 will be provided to investigation sites and administered once daily by mouth, or by NG tube or G-tube.

Date of first/last administration of study drug

The date of first administration of study drug is defined as the first date when a non-zero dose of study drug was administered and recorded on the Dosage Administration Record (DAR) eCRF. For the sake of simplicity, the date of first administration of study drug will also be referred as start date of study drug.

The date of last administration of study drug is defined as the last date when a non-zero dose of study drug was administered and recorded on DAR eCRF. This date will also be referred as last date of study drug.

Study day

The study day for all assessments (e.g. tumor assessment, death, disease progression, tumor response, performance status, adverse event onset, laboratory abnormality occurrence, vital sign measurement, dose interruption etc.) will be calculated using the start date of study drug as the origin. For assessments occurring after or on the start date of study drug, study day will be calculated as:

Study Day =Date of assessment/Event date - start date of study drug + 1.

The first day of study drug is therefore study day 1.

For any assessment or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) occurring prior to the start of the study drug, study day will be negative and will be calculated as:

Study Day = Date of assessment/Event date - start date of study drug.

The study day will be displayed in the data listings. If an event starts before the reference start date, the study day displayed on the listing will be negative.

Baseline

Baseline is the result of an investigation describing the “true” uninfluenced state of the patient. The last available assessment before or on the start date of study drug is defined as “baseline” value or “baseline” assessment, unless otherwise stated. If the assessment is planned to be performed prior to the first dose of study drug in the protocol and the assessment is performed on the same day as the first administration of study drug, it will be assumed that it was performed prior to study drug administration, if assessment time or first dose time is not collected or is missing. If assessment and first dose times are collected, the observed time point will be used to determine pre-dose on study day 1 for baseline calculation. Unscheduled assessments will be used in the determination of baseline. See Section 5.5.2 for further details on derivation of baseline for laboratory data and ECGs.

Patients who start treatment and discontinue from the study on the same day may have two different sets of data collected on study day 1, one being reported to the cycle 1 day 1 visit, the other reported to the end of treatment (EOT) visit. Data reported at the EOT visit are not eligible for baseline selection.

Cohort

A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time. There may be more than one cohort at the same dose level.

Treatment group

Treatment group will generally be determined by the initially planned LDK378 dose level in mg/m2 and regimen on Cycle 1 Day 1. For safety analysis, treatment group will be determined by dose and regimen received. Further details on the determination of treatment received is given in Section 2.2 A treatment group can include several cohorts of patients who have received the same dose level and regimen but were recruited at the different point during the study. A treatment group may consist of one or more cohorts.

2.2 Analysis sets

A patient is considered to be enrolled into the study if they have signed study informed consent. Only patients who have signed study informed consent prior to study procedures will be included in the analysis data sets.

Full analysis set

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

The planned treatment will be based on the first dosing record. The corresponding fasted/fed status will be determined as per Table 2-1 below as per protocol.

Table 2-1 Dose level and fasted/fed status

Dose Levels	Fasted/Fed Status
200 mg/m^2	Fasted
300 mg/m^2	Fasted
450 mg/m^2	Fasted
510 mg/m^2	Fasted
560 mg/m^2	Fasted
320 mg/m^2	Fed
400 mg/m^2	Fed
500 mg/m^2	Fed

Safety set

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

The patients will be classified according to treatment received, where treatment received is defined as:

1. The actual dose level (mg/m^2) is the planned dose level if any actual total daily dose administered is equal to the value of "the planned dose levels (Table 2-1) * BSA (m^2) rounds to the nearest 50 mg". For 25/75 mg, either rounding up or rounding down is acceptable.

2. The first actual dose level in the study (converts actual total daily dose administered / BSA (m^2) and maps to nearest planned dose levels) if the planned dose level was never received.

BSA = The last available BSA measurement on or before dosing date will be used in the calculation for actual dose level.

For example, if a patient from 500 mg/ m^2 fed group doesn't meet the first criteria, and the first actual dose level in the study is 150 mg. Suppose this patient has BSA=0.45 m^2 on/before the first dose, then the first actual dose level in the study=actual total daily dose administered / BSA (m^2)=333 mg/ m^2 , which will be rounded to the nearest planned dose level 320 mg/ m^2 fed.

Dose determining set

The dose determining analysis set (DDS) consists of all patients from the safety set who ***either*** meet the minimum exposure criterion and have sufficient safety evaluations ***or*** discontinue earlier due to DLT in the escalation phase.

A patient is considered to have met the minimum exposure criterion if s/he 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 and who did not discontinue earlier due to a DLT will be regarded as ineligible for the DDS.

Pharmacokinetic analysis set

The pharmacokinetic analysis set (PAS) consists of all patients who received at least one dose of LDK378 and have at least one evaluable pharmacokinetic (PK) sample.

Depending on whether the sample is part of a full profile or a trough collection, the specific criteria are listed as follows.

An evaluable full PK profile is defined as:

1. On the PK collection day, no vomiting occurred within 4 hours of dosing on the full PK sampling day (i.e., no vomiting within 4 hours after Cycle 1 Day 1 dose or after Cycle 2 Day 1 dose), AND
2. On the PK collection day, the patient takes study drug according to the originally assigned dose, AND
3. The patient takes study drug according to the originally assigned dose for at least 5 consecutive days without interruption or dose modification prior to the PK sampling day (except for Cycle 1 Day 1, i.e., only applicable to Cycle 2 Day 1), AND

4. On the PK collection day, the patient takes study drug under the originally assigned prandial condition, AND
5. The patient takes study drug under the originally assigned prandial conditions, i.e., dose administered without food for patients in the fasted cohort, or dose administered with light snack food for patients in the fed cohort, for at least 5 consecutive days prior to the PK sampling day (except for Cycle 1 Day 1, i.e., only applicable to Cycle 2 Day 1), AND Additionally, an entire profile can be considered non-evaluable as per scientific judgment of the clinical pharmacology expert even if the above criteria are fulfilled. Reason will be documented.

An evaluable trough PK concentration (Cmin) is defined as:

1. the patient takes study drug according to the originally assigned dose for at least 5 consecutive days prior to the PK sampling day (except for Cycle 1 Day 1 in dose escalation and expansion phases), AND no vomiting occurs within 4 hours following the last dose intake prior to the PK sample draw,
2. For the pre-dose or 24 hour post-dose sample, draw must occur between 0 to 6 hours before the dose that is immediately after, AND
3. The patient takes study drug under the originally assigned prandial conditions, i.e., dose administered without food for patients in the fasted cohort, or dose administered with light snack food for patients in the fed cohort, for at least 5 consecutive days prior to the PK sampling day (except for Cycle 1 Day 1), AND Additionally, a sample can be considered non-evaluable as per scientific judgment of the clinical pharmacology expert even if the above criteria are fulfilled. Reason will be documented.

A patient belongs to PAS if he/she has either an evaluable full PK profile or an evaluable trough PK sample.
Any blood samples missing blood collection date or time, or missing associated study drug dosing date or time will be excluded.

Frequency counts and percentages (using FAS as denominator) of patients in each of the above defined analysis sets will be summarized. In addition, listings of patients included in each of the analysis sets will be provided.
Section 2.3.5 provides further details regarding the derivation of the analysis sets.

2.3 Patient disposition, demographics and other baseline characteristics

The FAS will be used for all patient demographic and baseline characteristic summaries and listings, unless otherwise specified.

Basic demographic and background data

All demographic and baseline disease characteristics data will be summarized and listed for all patients. Categorical data (e.g. gender; age groups: 1 year to <7 years, 7 years to <12 years, 12 years to <18 years; race; ethnicity; Karnofsky or Lansky performance status) will be summarized by frequency count and percentages. Continuous data (i.e. age, weight, height, body surface area) will be summarized by descriptive statistics (as defined in Section 2.1).

All data collected during the baseline evaluation will be listed.

Diagnosis and extent of cancer

Descriptive statistics and frequency counts and percentages will be tabulated, as appropriate, for diagnosis and extent of cancer based on the data collected on the eCRF including primary site of cancer, time (in months) from initial diagnosis of primary site to start date of study drug, time (in months) since most recent recurrence/relapse or progression to start date of study drug, current extent of disease (metastatic sites), types of lesions (target and non-target lesions) at baseline, and disease burden at baseline for target lesion. Note: Presence/absence of target and non-target lesions will be based on the data collected on RECIST target/non-target lesion assessment eCRF pages. Presence/absence of index and non-index lesions will be based on the data collected on Lymphoma index/non-index lesion assessment eCRF pages. Metastatic sites will be based on diagnosis page.

ALK status

If ALK status is not already known, patients will be tested for ALK positive status using a Novartis designated central laboratory. ALK status from local and central laboratory results at baseline as determined in the retrospective collection of pathological reports will be summarized using frequency counts and percentages for patients. The ALK status summary includes test result (positive, negative, not evaluable), ALK abnormality type (ALK translocation, ALK amplification, ALK point mutation, other), test methodology used (FISH, IHC, RT-PCR, sequencing DNA/RNA, other).

All other ALK data collected during the baseline evaluation will be listed.

Medical history

Medical history and current medical conditions, including cancer-related conditions and symptoms will be summarized and listed. Separate summaries will be presented for ongoing and historical medical conditions. The summaries will be presented by primary system organ class (SOC) and preferred term (PT). Medical history and current medical conditions are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Protocol deviations

Frequency counts and percentages of patients in the FAS with any protocol deviations (inclusion/exclusion criteria not met, patient not withdrawn as per protocol, key procedures not performed as per protocol, treatment deviation, prohibited concomitant medication, Good Clinical Practice (GCP) deviation) will be tabulated by the deviation category. The full list of protocol deviations are documented in the Data Handling Plan (DHP). All protocol deviations will be listed.

Prior antineoplastic therapy

Prior anti-neoplastic (anti-cancer) therapy will be listed in three separate categories: (i) medications, (ii) radiotherapy, and (iii) surgery.

The number and percentage of patients who received any prior anti-neoplastic medications, prior anti-neoplastic radiotherapy or prior anti-neoplastic surgery will be summarized.

The summary of prior anti-neoplastic medications will include the total number of regimen, setting at last medication, the time between end of last medication to start of treatment in days (end of last medication is based on end date of last dose, the best response at last medication (defined to be the best response during the last treatment regimen recorded), and time (in months) from start of last medication to progression. The last medication is defined taking into account the end date. Prior antineoplastic medications will also be summarized by ATC class, and preferred term.

The summary of prior anti-neoplastic radiotherapy will include a summary of radiotherapy locations, including all locations recorded for each patient. Setting, method, and best response at last radiotherapy will also be summarized.

The summary of prior anti-neoplastic surgery (excluding diagnostic biopsies) will include the time between the last surgery to start of treatment, procedure at last surgery and residual disease at last surgery.

2.3.1 Patient disposition

Screen failures

Screen failures will comprise patients who have been enrolled and signed study ICF, and screened to the study and have failed to meet inclusion or exclusion criteria. These patients are not treated with study drug. Frequency counts and percentages will be tabulated for all enrolled patients as follows:

- Number (%) of patients who completed screening phase (based on the presence of 'Screening log' and 'Demography' page);
- Number (%) of patients who discontinued during screening phase (based on the presence of discontinuation reason entered and 'Will the subject enter the study' is 'No' in the 'Screening log' page) ;
- Reasons for screening phase discontinuation (based on reasons recorded in Screening log' page).

All screen failure patients with reasons for screen failure will be listed.

Patient Disposition

The FAS will be used for the patient disposition summary tables and listings. The following will be tabulated:

- Number (%) of patients who are still ongoing-treatment (based on the absence of the 'End of Treatment' page);
- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment' page with date of discontinuation and reason of discontinuation entered);
- Primary reasons for study treatment discontinuation (based on discontinuation reasons entered in the 'End of Treatment' page);
- Number (%) of patients who discontinued from study (based on completion of 'Study evaluation completion' page);

- Number (%) of patients who discontinued treatment but continued to be followed (based on completion of 'End of Treatment' page and 'Study evaluation completion' page not completed);
- Primary reasons for study evaluation completion (based on primary reason for study evaluation completion in the 'Study evaluation completion' page).

2.4 Treatments (study treatment, concomitant therapies, compliance)

The study drug and the study treatment is LDK378, as in the previous sections, reporting was based on FAS. The Safety Set will be used for all medication data summaries and listings unless otherwise specified.

2.4.1 Study treatment / compliance

Dose exposure and intensity

The Safety set will be used for summaries and listings of dose exposure and intensity unless otherwise specified.

Definitions of duration of exposure, cumulative dose, average daily dose, actual dose intensity (DI), planned dose intensity (PDI), relative dose intensity (RDI), percentage of days dosed, percentage of days the planned/intended dose was received, as well as intermediate calculations, include:

- Duration of exposure (days): last date of study drug − first date of study drug + 1 (periods of interruption are not excluded)
- Cumulative dose (mg): total dose of study drug taken by a patient in the study
- Number of dosing days (days): duration of exposure − number of zero dose days
- % Days dosed: 100×number of dosing days/duration of exposure (days)
- % Days with planned dose: 100× number of days with planned dose/duration of exposure (days)
- Average daily dose (mg/day): cumulative dose (mg)/number of dosing days (days)
- DI (mg/day): cumulative dose (mg)/duration of exposure (days)
- PDI (mg/day): cumulative planned dose (mg) / duration of exposure (day)
- RDI (%): 100 × DI (mg/day)/PDI (mg/day)

Duration of exposure to study drug, cumulative dose, and percentage of actual days dosed, percentage of days the planned/intended average daily dose was received, DI and RDI will be summarized. In addition, the duration of exposure to study drug will be categorized into time intervals); frequency counts and percentages of patients with exposure in each time interval will be presented. Frequency counts and percentages of patients who have dose reductions or interruptions, and the corresponding reasons, will be provided. The number of dose interruptions per patient, and the duration of dose interruptions (days) will be summarized. Cumulative dose, dose intensity and relative dose intensity of LDK378 will be listed by patient. Categories for relative dose intensity of LDK378 will be specified as < 0.5, ≥ 0.5 - < 0.75, $\geq$

0.75 - < 0.9, ≥ 0.9 - < 1.1 and ≥ 1.1. The number and proportion of patients within each category will be presented.

Listings of all doses of the study drug along with dose change/interruption reasons will be produced.

2.4.2 Concomitant and post therapies

The Safety set will be used for the summaries and listings of concomitant and post therapies unless otherwise specified.

Concomitant therapy

Concomitant therapies are defined as any medications (excluding study drug, prior antineoplastic treatments) and significant non-drug therapies (including physical therapy and blood transfusions) administered in the study and recorded in the Concomitant Medications/significant non-drug therapies eCRF.

These therapies will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (WHO ATC) classification system. All summaries will be tabulated using frequency counts and percentages.

Concomitant therapies will be summarized by ATC class and preferred term. These summaries will include 1) medications and non-drug therapies starting on or after the start of study drug but starting no later than 30 days after last dose of study drug and 2) medications and non-drug therapies starting prior to the start of study drug but continuing after the start of study drug.

All therapies will be listed. Any therapies starting and ending prior to the start of study drug or starting more than 30 days after the last date of study drug will be flagged in the listing.

Frequency and percentage of patients using medications known to prolong the QT interval concomitantly with study drug will be summarized by ATC class and preferred term.

Antineoplastic therapy after discontinuation of study drug

All summaries will be tabulated using frequency counts and percentages using the FAS.

Antineoplastic therapies, including medications, surgeries, and radiotherapies, initiated after discontinuation of study drug will be summarized and listed by Anatomical Therapeutic Chemical (ATC) class and preferred term.

2.5 Analysis of the primary objective

The primary objective of the study is to estimate the MTD/RDE separately on a daily dose of LDK378 when administered orally as a single agent to pediatric patients with an advanced malignancy carrying genetic alteration of ALK. 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). The MTD/RDE is determined to be 510 mg/m2 for fasted regimen and 500 mg/m2 for fed regimen.

2.5.1 Primary endpoint

Variable

The primary endpoint is the incidence of dose limiting toxicities (DLTs) in Cycle 1.The MTD is defined as the maximum dose for a given schedule that is expected to cause DLTs in no more than 33% of patients during the first cycle of treatment. Estimation of the MTD during the dose-escalation phase of the study will be based upon the estimation of the probability distribution of the incidence of DLT in cycle 1 in patients in the dose-determining set.

2.5.2 Statistical hypothesis, model, and method of analysis

An adaptive BLRM with two parameters guided by the EWOC principle will be used to make dose recommendations and estimate the MTD separately during the fasted dose escalation and the fed dose escalation of the study.

Statistical model for the fasted dose escalation

The dose-toxicity (DLT) relationship in the fasted dose-escalation phase 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 $\text{logit}(\pi_{(d)}) = \ln(\pi_{(d)}/(1-\pi_{(d)}))$, $\pi_{(d)}$ is the probability of a DLT at dose d. Doses are rescaled as d/d* with reference dose $d^* = 400$ mg/m^2 of LDK378. Consequently 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 Bayesian approach requires the specification of prior distributions for the model parameters.

See Section 14.1.2 of the protocol for the prior specification for the fasted dose escalation.

Statistical model for the fed dose escalation

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. 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.

Methodology for updating down-weighting:

Since fed patients will be enrolled after all the patients in dose escalation fasted part will have potentially completed cycle 1 (or have experienced DLT), and since it can be assumed that there is a certain grade of similarity in dose toxicity relationship between these two regimen, the updating of the prior distribution of the BLRM parameters for fed patients will be evidence based. In particular, at the time of starting the fed-patients cohort, DLT data from fasting patients will be included into the BLRM and discounted (assuming substantial between regimen heterogeneity) to account for potential differences between fed and non-fed patients, while assuming some degree of similarity.

Specifically, the DLT information from fasted patients will be incorporated through down-weighting the data directly. The weight "*w*" (see Neuenschwander et al 2010) that will be assigned to each fasted patient included in the DDS is given in the following formula:

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

where n is the sample size of historical data (i.e. the number of fasted patients in the DDS), σ is the "outcome standard deviation" for one observation and τ is the assumed between regimen standard deviation. n^*_∞ can be interpreted as the maximum prior effective sample size under infinite historical information. σ was chosen as 2 and τ was set as 2, to correspond to a substantial heterogeneity due to the different dosing regimens.

When all patients in the fasted dose escalation have completed at least one cycle, the weights will be calculated based on the data available at that time point.

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/m2, and to 25% after reaching 450 mg/m2, 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. 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 of the study protocol.

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, and review of the clinical data. 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.

2.6 Analysis[SP1] of the secondary objectives

A secondary objective of this study is to assess the anti-tumor activity of LDK378 in fasting and fed states. The primary evaluation of the anti-tumor activity of LDK378 will be based on investigator assessment of response (Overall Response Rate, Progression-Free Survival, and Duration of Response) using the FAS per RECIST 1.1 for patients with neuroblastoma and other solid tumors, and IWG criteria for patients with lymphoma. In patients with neuroblastoma, disease assessable at screening only by MIBG scans and by bone marrow evaluation will be treated as non-target lesions. MIBG response will be listed.

Overall Response rate

ORR is defined as the proportion of patients with a best overall response (BOR) of complete response (CR) or partial response (PR) for RECIST. For CHESON: 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). ORR will be summarized by indication and by treatment group, where the patients are pooled from both the dose escalation and expansion phases for MTD / RDE determined for each regimen, and exact 95% confidence intervals will be presented.

In addition, for the expansion group patients with ALK activated neuroblastoma, a Bayesian approach will be used to estimate the ORR based on RECIST 1.1 data, 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. ≤ 2 CR or PR out of 25), then insufficient antitumor activity will be declared.

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.

Best Overall Response

Best overall response (BOR) is the best response recorded from the start of the treatment until disease progression. Patients with a BOR of 'UNKNOWN' will be treated as non-responders when estimating ORR. If any non-palliative cancer therapy is taken while on study any subsequent assessments will be excluded from the BOR determination. MIBG response score per curie criteria will be recorded and listed for patients with neuroblastoma who had MIBG scan.

Determination of BOR per RECIST 1.1

ORR is defined as the proportion of patients with a best overall complete response (CR) or partial response (PR) per RECIST 1.1.

For patients with the primary diagnosis other than lymphoma, BOR will be based on the overall lesion assessment per RECIST 1.1. 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 (for details see Protocol Appendix 5).

The BOR 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
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR)
- SD = at least one SD assessment (or better)> 29 days after start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 85 days after start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 29 days or early progression within the first 85 days).

Determination of BOR per IWG criteria

For patients with the primary diagnosis of lymphoma, BOR will be based on the overall lesion assessment and disease response assessment per IWG (Cheson) response criteria. See Section 14.6 of protocol for guideline for efficacy evaluation in lymphoma patients based on IWG (Cheson) response criteria.

The BOR for each patient is determined from the sequence of overall radiological responses and overall disease responses according to the following rules:

- CR = at least one overall disease response of CR
- PR = at least one overall radiological response or overall disease response of PR (and not qualifying for CR)
- SD = at least one SD overall radiological response > 29 days after start of treatment (and not qualifying for CR or PR)
- PD = progression ≤ 85 days after start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases.

In general, in the determination of BOR, 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 this assignment must stay the same or improve over time until progression sets in, with the exception of an UNK status.

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

Duration of response

Among patients with a confirmed PR or CR per RECIST 1.1 or with a response (CR or PR) per IWG criteria, DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression (PD) or death due to any cause.

DOR will be described separately by indication and by treatment group, and by expansion group in tabular and graphical format for patients treated at MTD/RDE by expansion group, using Kaplan-Meier methods including estimated median (in months) with 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997and Kaplan-Meier estimated probabilities with corresponding 95% CIs (Kalbfleisch and Prentice 1980) at several time points (including at least 2, 4, 6, 8, 10, 14 months).

2.7 Analysis of other secondary efficacy objectives

Progression-free survival

PFS is defined as the time from the start date of study drug to the date of the first radiologically documented PD or death due to any cause per RECIST 1.1, for patients with solid tumor; and from the start date of study drug to the date of the first PD as overall disease response or death due to any cause per Cheson, for patients with lymphoma.

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any further anticancer therapy, PFS will be censored at the date of the last adequate tumor evaluation before the cut-off date or before the start of the new anticancer therapy date, whichever is earlier. Clinical deterioration will not be considered as a qualifying event for progression.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs:

1: Ongoing without event

2: Lost to follow-up

3: Withdrew consent
4: Adequate assessment no longer available
5: Initiation of new cancer therapy prior to progression
6: Event after >=2 missing tumor assessments

PFS will be described in tabular and graphical format for patients treated at MTD/RDE by expansion (disease) group, and also by indication and by treatment group using Kaplan-Meier methods as described for DOR, including estimated median (in months) with 95% CI, 25th and 75th percentiles and Kaplan-Meier estimated probabilities with corresponding 95% CIs at several time points (including at least 2, 4, 6, 8, 10, 14 months). Censoring reasons will also be summarized. Also duration between treatment start date and cut-off date, and PFS follow-up time will be summarized by expansion, and also by indication and by treatment group.

2.8 Safety analyses

The safety set will be used for all safety analyses with the exception of the DLT analyses that will use the DDS.

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

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study drug
- On-treatment period:
  - For discontinued patients, from day of first dose of study drug to 30 days after last dose of study drug
  - For ongoing patients, from day of first dose of study drug to the data cut-off date
- Post-treatment period: starting at day 31 days after last dose of study drug

The safety summary tables will include only assessments collected no later than 30 days after study drug discontinuation and assessments prior to the data cut-off date for on-going patients, unless otherwise specified.

For select items, shift tables or change from baseline summaries generated for laboratory, ECG, vital signs and change score (including Karnofsky/Lansky) generation may use data from pre-treatment period for baseline calculations.

All data, regardless of observation period, will be listed and visits/cycles collected in the pre-treatment or post-treatment period will be displayed in all the listings.

2.8.1 Adverse events (AEs)

AEs will be coded using the latest version of MedDRA available prior to clinical database lock and will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading criteria exists for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life threatening, respectively, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected on the "End of Treatment" or "Study evaluation completion" eCRF pages.

All AE summaries will be summarized (frequency counts and percentages) by system organ class and/or preferred term, and maximum severity grades, except where otherwise noted. A patient with multiple CTC grades for an AE will be summarized under the maximum CTC grade recorded for the event.

The following AE summaries will be produced:

- AEs regardless of study drug relationship
- AEs suspected to be study drug related
- All deaths, by primary SOC and PT
- On-treatment deaths, by primary system organ class and preferred term
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- AEs associated with study drug discontinuation
- AEs requiring dose adjustment or interruption
- AEs requiring significant additional therapy
- AEs excluding SAEs
- In addition, AEs regardless of study drug relationship will be summarized by PT and age group for MTD/RDE patients.

2.8.1.1 Adverse events of special interest

Adverse events of special interest (AESIs) are defined as AEs within the following categories/ groupings of preferred terms:

- Hepatotoxicity
- Interstitial lung disease/Pneumonitis
- QT prolongation
- Hyperglycemia
- Bradycardia
- GI toxicity (nausea, diarrhea, vomiting)
- Pancreatitis (including Lipase or amylase increases)

AESIs are defined at the project level and may be updated based on emergent data to reflect new AESIs of interest at the time of analysis. The AESIs listed above will be identified based on a list of preferred terms. The list of preferred terms will be finalized in a separate document.

Frequency counts and percentages of patients with DLTs will be tabulated by treatment group based on the DDS. DLTs will be listed by treatment group and patient.

2.8.2 Laboratory data

The summaries will include all laboratory assessments collected no later than 30 days after last dose of study drug. All laboratory assessments will be listed and those collected later than 30 days after study drug discontinuation will be flagged in the listings. For laboratory data assessments, data from all sources (central and local laboratories) will be combined.

Laboratory data will be classified (by Novartis Oncology CDRR) into CTC grades according to the National Cancer Institute (NCI) CTCAE v4.03. For all reports, CTC grade is always obtained on the converted measurement in SI unit. Grade 5 will not be used. The CTC grade 0 will be assigned as below in different scenarios:

1. For lab parameters defined by criteria based on normal range only, a severity grade of 0 will be assigned when the value is within normal limits.
2. For lab parameters whose grade is defined by criteria based on normal range and absolute values (e.g. platelet count decrease). A severity grade of 0 will be assigned when the value is within normal limits.
3. For lab parameters whose grade is defined by criteria based on normal range and the change from baseline value, with no other associated clinical criteria such as concomitant medication (e.g. creatinine increased) the following will be applied. For the baseline grading and for the grading of post-baseline laboratory values with missing baseline grading, the grade will be derived using the criteria based only on the normal range as per CTCAE v4.03. A severity grade of 0 will be assigned when the post-baseline value is ≤ ULN (for hyper) or ≥ LLN (for hypo).

Parameters for which a grading does not exist will be classified into low/normal/high group by means of laboratory normal ranges.

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

- Shift tables using CTC grades to compare baseline to the worst post-baseline value for laboratory parameters with CTC grades.
- Shift tables using low, normal, high (as well as low and high combined) classifications to compare baseline to the worst post-baseline value for laboratory parameters where CTC grades are not defined.

Liver function tests (LFTs) of interest for LDK378 are total bilirubin (TBILI), ALT, AST and ALP. In what follows, AT refers to ALT or AST values. LFTs will be summarized as follows:

- Shift tables of baseline vs. worst post-baseline on-treatment values for the categories:
  - TBILI ≤ 2xULN, TBILI > 2xULN and missing TBILI
  - ALT ≤ 3xULN, ALT > 3xULN and missing ALT
  - AST ≤ 3xULN, AST > 3xULN and missing AST
  - ALP < 2xULN, ALP ≥ 2xULN and missing ALP
- Frequency counts and percentages of patients with worst post-baseline on-treatment values in the categories:
  - ALT > 3xULN, ALT > 5xULN, ALT > 10xULN, ALT > 20xULN
  - AST > 3xULN, AST > 5xULN, AST > 10xULN, AST > 20xULN
  - AT > 3xULN, AT > 5xULN, AT > 10xULN, AT > 20xULN
  - TBILI > 2xULN

- Concurrent ALT > 3xULN and TBILI > 2xULN
- Concurrent AST > 3xULN and TBILI > 2xULN
- Concurrent AT > 3xULN and TBILI > 2xULN
- Concurrent AT > 3xULN and TBILI > 2xULN and ALP < 2xULN
- Concurrent AT > 3xULN and TBILI > 2xULN and ALP ≥ 2xULN

Concurrent measurements are those occurring on the same date.

In addition, a listing of all TBILI, ALT, AST and ALP values for patients with a post-baseline TBILI > 2xULN, ALT> 3xULN or AST > 3xULN will be provided.

The following listings will be produced by laboratory parameter, treatment group, and patient for all laboratory parameters where CTC grades are defined:

- Listing of patients with laboratory abnormalities of CTC grade 3 or 4
- Listing of all laboratory data with values flagged to show the corresponding CTC grades and the classifications relative to the laboratory reference ranges.

2.8.3 Other safety data

2.8.3.1 ECG and cardiac imaging data

ECG data will be analysed based on central laboratory reported results. The summaries will include all ECG assessments performed no later than 30 days after the last date of study drug. All ECG assessments will be listed, and those collected later than 30 days after on treatment period will be flagged in the listing.

Selecting Primary QT Correction for Heart Rate

The analysis of QT data is complicated by the fact that the QT interval is highly correlated with heart rate. Because of this correlation, formulas are routinely used to obtain a corrected value, denoted QTc, which is independent of heart rate. This QTc interval is intended to represent the QT interval at a standardized heart rate. Several correction formulas have been proposed in the literature. For this analysis we will use some of those methods of correction, as described below. The QT interval corrected for heart rate by the Bazett's formula, QTcB, is defined as

$$QTcB = \frac{QT}{\sqrt{RR}},$$

the QT interval corrected for heart rate by the Fridericia's formula, QTcF, is defined as

$$QTcF = \frac{QT}{\sqrt[3]{RR}},$$

where RR represents the RR interval of the ECG, in seconds.

Although Bazett's correction is the historical standard, it does not perform well when heart rate fluctuates. Fridericia's formula may perform better under these conditions. An alternate correction to achieve the goal of getting uncorrelated QTc and RR is based on linear regression methods which yield, theoretically, uncorrelated QTc and RR.

Linear regression method:

- Fit a model QT = a + b * RR to baseline data
- Use the estimated slope, $\hat{b}$, to correct QT
- Corrected QT for heart rate will be computed as follows:

$$QTcP = QT + \hat{b}*(1- RR)$$

Data will be summarized using QTcF and QTcB. However, if these are not appropriate for the data set due to an observed large correlation between corrected QT and HR using the baseline assessments, the results will also be summarized using QTcP.

ECG Summaries

The following analyses will be performed for each applicable ECG parameters (RR, PR, QRS, QT, ventricular rate -denoted as HR in what follows-, and QTc) as noted.

- Pearson correlation between QT and RR, QTc (QTcB, QTcF and, if applicable, QTcP) and HR using individual (non-averaged) baseline assessments and separately using on-treatment assessments
- For each of the ECG parameters (HR, and QTc, QT, QRS and PR intervals) descriptive statistics at baseline, at each post-baseline time point and changes from baseline at each post-baseline time point
- For each of the QTc and QT intervals, shift tables based on notable parameter categories (≤450, >450 - ≤480, >480 - ≤500, >500 ms) at baseline and the worst post-baseline value observed

The number and percentage of subjects with notable ECG values will be presented by treatment arm.

  - QT parameter (QT, QTc) increase from baseline >30 ms, >60 ms
  - Newly occurring post-baseline QT parameter > 450 ms, > 480 ms, > 500 ms
  - HR increase from baseline > 25% and value > 100 bpm
  - HR decrease from baseline > 25% and value < 50 bpm
  - PR increase from baseline > 25% and value > 200 ms
  - Newly occurring post-baseline PR > 200 ms and ≤220 ms, > 220 ms
  - QRS increase from baseline > 25% and value > 110 ms
  - Newly occurring post-baseline QRS > 110 ms and ≤ 120 ms, > 120 ms

  The denominator to calculate percentages for each category is the number of patients with both a baseline and a post-baseline evaluation. A newly occurring post-baseline ECG notable value is defined as a post-baseline value that meets the criterion post-baseline but did not meet the criterion at baseline

- Frequency counts and percentages of patients with newly occurring post-baseline qualitative ECG abnormalities (morphology) will be summarized. The denominator to calculate percentages for any newly occurring ECG abnormality, each abnormality type and each individual finding is the number of patients with both a baseline and a post-baseline

evaluation, and baseline being normal, i.e. those patients who are at risk of developing this abnormality. A newly occurring post-baseline qualitative ECG abnormality is defined as a post-baseline abnormal finding which was not present at baseline

Patients with notable ECG interval values and newly occurring qualitative ECG abnormalities will be listed by treatment group, , patient and timepoint, and the corresponding notable values and abnormality findings will be included in the listings.

Unscheduled ECG measurements will not be used in computing the descriptive statistics for change from baseline at each post-baseline time point. However, they will be used in the analysis of notable ECG changes and the analysis of notable QT parameters.

2.8.3.2 Vital signs

Vital sign assessments will be performed in order to characterize basic body function. The parameters collected are weight (kg), body temperature (°C), pulse rate (beats per minute), systolic and diastolic blood pressure (mmHg).
Vital signs shift table based on values classified as notable low, normal, notable high or notable (high and low) at baseline and worst post-baseline will be produced for pulse rate.

Patients with clinically notable vital sign abnormalities will be listed. All vital sign assessments will be listed by patient and vital sign parameter. In the listings, clinically notable values will also be flagged.
The criteria for clinically notable values are defined in Table 2-2.

Table 2-2 Clinically notable vital sign ranges.

Body temperature (°C)	High	≥39.1°C	
	Low	≤35.0°C	
Weight	High	Increase from baseline ≥ 10%	
	Low	Decrease from baseline ≥ 10%	
Pulse rate (beats per minute)	High[2]	12-18 months	> 140
		18-24 months	> 135
		2-3 years	> 128
		3-4 years	> 123
		4-6 years	> 117
		6-8 years	> 111
		8-12 years	> 103
		12-15 years	> 96
		15-18 years	> 92
	Low[2]	12-18 months	< 103
		18-24 months	< 98
		2-3 years	< 92
		3-4 years	< 86
		4-6 years	< 81
		6-8 years	< 74

	8-12 years	< 67
	12-15 years	< 62
	15-18 years	< 58

[1]Systolic and diastolic blood pressure will be listed individually.

[2]Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. Lancet 2011; published online March 15. DOI: 10.1016/S0140-6736(10)62226-X.

2.9 Performance status

Performance status will be assessed using the Karnofsky or Lansky performance scales, depending on the patient's age. The score, reported on an ordinal scale of 0-100 provides a rough measure of the patients' well-being, including ability to conduct activities of daily living and functional capacity. Patients are classified as to their functional impairment status using the Karnofsky performance assessment (patients greater than 12years of age) or the Lansky performance status (patients 12 years of age and younger). The definition of scores in relation to performance based on the Karnofsky performance assessment is given in Table 2-3. The definition of scores based on the Lansky performance assessment is given in Table 2-4.

Table 2-3 Karnofsky performance status scale (for patients greater than 12yrs of age)

General category	Grade	Karnofsky score interpretation
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

Table 2-4 Lansky score (for patients 12years of age and younger)

General category.	Score	Lansky status
Able to carry on normal activity and to work; no special care needed	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

General category.	Score	Lansky status
Mild to moderate restriction	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
Moderate to severe restriction/dead	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

Performance status will be summarized separately for the Karnofsky and the Lansky score based on FAS. Shift tables of scores at baseline to worst post-baseline status by general category will summarized. Performance status at each time point will be listed.

2.10 Pharmacokinetic endpoints

Blood samples for PK analysis of ceritinib are collected during the dose escalation part and expansion part of the study as per protocol. All PK analyses will be performed based on the PAS unless otherwise specified.

During the dose escalation phase of the study, blood samples for full plasma concentration-time profile of ceritinib are collected over 24 hours on Cycle 1 Day 1 and on Cycle 2 Day 1 at the following scheduled time points: pre-dose, 2, 4, 6 and 24 hours post-dose. Trough PK samples are also collected pre-dose on Day 1 of Cycle 3-4 and Day 15 of Cycle 1.

During the expansion phase, blood samples for full plasma concentration-time profile of ceritinib are collected over 24 hours on Cycle 2 Day 1 at the following scheduled time points: pre-dose, 2, 4, 6 and 24 hours post-dose. Trough PK samples will be collected on Day 1 of Cycle 1-4 at the MTD and/or RDE.

Only PK plasma concentrations with non-missing sampling data and time, and for which the last dose date and time prior to the PK sample draw are non-missing will be included in the PK analysis. Unscheduled samples are not included in any analysis, but these samples will be listed using PAS and flagged in the corresponding concentration listing.

PK parameters

Pharmacokinetic parameters will be determined using non-compartmental method(s), using Phoenix WinNonlin (Pharsight, Mountain View, CA.), The PK parameters listed in Table 2-6 will be estimated and reported, as appropriate.

Among the parameters, the following are considered primary: AUCtau, Cmin, Cmax, Tmax ; and the following are considered secondary: CLss/F, Racc. Those not designated as primary or secondary will be listed only.

Table 2-5 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

Data handling principles

Concentration values below the lower limit of quantitation (LLOQ) (< 1.0 ng/mL) will be displayed in listings as zero with a flag and handled as zero in the calculations of summary statistics except for geometric means and associated CVs where they will be set to missing Any missing PK parameters will not be imputed.

LDK378 concentrations

Summary statistics, including n, mean, SD, coefficient of variation CV (%) for mean, geometric mean, geometric CV (%), median, minimum and maximum, will be presented for evaluable PK plasma concentration of LDK378 following the general reporting rule for PK, by treatment and scheduled time point for both full PK profile and trough PK concentrations, separately for fasted and fed patients and for escalation phase and expansion phase. For patients with full PK profile on Cycle 1 Day 1 or Cycle 2 Day 1, corresponding graphical presentations of the plasma concentration profiles will be provided by treatment using arithmetic mean (+/- SD) and geometric mean values at each scheduled time point. The individual plot will also be provided.

LDK378 PK parameters

Primary and secondary PK parameters will be summarized using the same reporting approach as for LDK378 concentrations, by treatment, separately for Cycle 1 Day 1 and Cycle 2 Day 1 for fasted and fed patients in the escalation and expansion phase. For Tmax, only median, minimum and maximum will be presented.

All PK parameters and concentration data will be listed by treatment using PAS.

Dose proportionality (DP) analysis

DP analysis at single dose (Cycle 1 Day 1) and steady state (Cycle 2 Day 1): Data from both dose-escalation phase and expansion phase will be used. AUC0-24h and Cmax will be analyzed. All dose levels will be included.

DP will be assessed via the following model as well as graphical presentations.

DP is analyzed by fitting a linear model as described below.

$$\ln(PK) = \alpha + \beta * \ln(\text{actual dose}),)$$

where PK is the PK parameter, AUC0-24 or Cmax, and actual dose (mg/m2) is defined as dose divided by BSA.

The estimate and its 90% confidence interval (CIs) for β in each case are reported. As an informal comparison, the estimates and CIs for β are compared to the target dose-proportionality range, calculated by the following formula (Smith, 2000).

Lower bound of target dose-proportionality range of β: 1 + ln(0.8)/ln(dose range)

Upper bound of target dose-proportionality range of β: 1 + ln(1.25)/ln(dose range)

Dose range is the highest actual dose/lowest actual dose, for which data are used for the dose proportionality analysis. The dose range may or may not be the same for all parameters.

This analysis is not prospectively powered for the result to fall into the target range, and therefore the actual result rather than the comparison itself should be emphasized when interpreting data.

Trough concentration (Ctrough)

Trough PK samples will be collected at the following time points:

- 0 hour pre-dose samples on C1D1, C1D8, C1D15, C2D1-C6D1 in all patients
- 0 hour pre-dose sample on C1D2 (i.e. 24 hour post-dose samples on C1D1), and C2D2 (i.e.

24 hour post-dose samples on C2D1) for patients with full PK collection
The trough concentrations obtained throughout the study will be plotted over time by treatment arm using PAS. Only time points with n ≥ 4 trough observations will be shown on the figure.

No model-based analyses will be conducted.

Average Ctrough

Average trough concentration will be used in the exposure response analyses. Each patient may have one or more Ctrough values. The average Ctrough considering the distribution of PK is generally lognormal is defined as:
$Ctrough_{avg} = geometric\ mean\ (all\ Ctrough\ for\ each\ patient)$, considering the distribution of PK concentration is generally lognormal.
Ceritinib trough concentration included in calculating the average **must fulfill** the following rules:

- For the pre-dose or 24 hour post-dose sample, draw must occur between 18 to 30 hours

after the last dose intake (except for Cycle 1 Day 1), AND

- For the pre-dose or 24 hour post-dose sample, the draw must occur before the next dose

intake, AND

- Additionally, a sample can be considered non-evaluable as per scientific judgment of the

clinical pharmacology expert even if the above criteria are fulfilled. Reason will be documented.

The criteria have been modified over evaluable trough concentration as defined in PAS by removing the following three rules:

- No vomiting occurs within 4 hours following the last dose intake prior to the PK sample

draw,

- The patient takes study drug according to the originally assigned dose for at least 5 consecutive days without interruption or dose modification prior to the PK sampling day

(except for Cycle 1 Day 1),

- The patient takes study drug under the originally assigned prandial conditions, i.e., dose

administered without food for patients randomized to the treatment arm of 750 mg fasted, or dose administered with food for patients randomized to the treatment arm of 450 mg with low-fat meal or 600 mg with low-fat meal, for at least 5 consecutive days prior to the PK sampling day (except for Cycle 1 Day 1)
This allows exposure-response analyses to take into account the exposure after study drug interruption, dose reduction, vomiting or fail to adhere to the assigned prandial condition for individual patient.

Quartile ranges of Ctrough_avg are defined as:

<Q1: $<25^{th}$ percentile
Q1-<Q2: $\geq 25^{th}$ percentile and $<50^{th}$ percentile
Q2-<Q3: $\geq 50^{th}$ percentile and $<75^{th}$ percentile
≥Q3: $\geq 75^{th}$ percentile

Ctrough_avg and its quartile values will be used in display of AE.

Inter and intra patient variation

The intra-patient and inter-patient variations will be evaluated using data from patients at MTD with one or more than one evaluable steady state trough PK measurements. Evaluable trough concentration is defined in PAS. For steady state trough concentration, we will only consider trough values collected on or after C1D15 (C1D1 sample will not be used in the analysis). The intra-patient and inter-patient variations will be estimated using random effects model with treatment as a fixed effect and patient as a random effect. See Section 5.7 for more details.

2.11 Patient-reported outcomes

Not applicable

[redacted]

2.13 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.

3 Sample size calculation

Dose escalation part

Respectively for the fasted dose escalation and the fed dose escalation, cohorts of 3 to 6 evaluable patients will be dosed in the dose-escalation part including at least 6 patients at the corresponding MTD/RDE level, as described in Section 6.2.3 of protocol. 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 12 for the fed dose escalation are expected to be treated in the dose escalation part, for the model to have reasonable operating characteristics relating to its MTD recommendation.

Dose expansion part

During the expansion part, approximately 45 patients will be treated on the preferred regimen (including all patients treated at the MTD/RDE on the preferred regimen during the dose escalation part 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 of protocol, 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 five 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.

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%.

4 Change to protocol specified analyses

Table 4-1 summarizes the changes to protocol-specified analyses and associated rationale for inclusion.

Table 4-1 Changes to protocol specified analysis or descriptions and rationale

Protocol Section	Protocol Description	Change
3.1 Best overall response	BOR for each patient will be determined based on the following rule: • SD = at least one SD assessment (or better) > 6 weeks after randomization (and not qualifying for CR or PR). • PD = progression ≤ 12 weeks after randomization (and not qualifying for CR, PR or SD).	BOR for each patient will be determined based on the following rule: • SD = at least one SD assessment (or better) > 29 days after randomization (and not qualifying for CR or PR). • PD = progression ≤ 85 days after randomization (and not qualifying for CR, PR or SD). This update was made to account for the +/-1 week window for the tumor assessment protocol defined schedule of 6 weeks. Consequently, BOR of 'Unknown' derivations of 'SD too early' and 'PD too late' will be based on the updated calculations: • Stable disease (SD) too early (≤ 29 days after randomization date) • PD too late (> 85 days after randomization date). See details in section 2.6.
3.1 Best overall response	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.	For the BOR calculation, the default option will not be used, i.e., assessments taken more than the 30 days after the last dose of study treatment will be included in the best overall response derivation for consistency with other time to event end-points.

5 Appendix

The sections below contain additional details on statistical methodology that will be included in Appendix 16.1.9 (Documentation of Statistical Methods) of the CSR as well as rules details on programing rules that will be followed to implement the analyses described in Section 2.

5.1 Data included in the analyses

This section provides additional details to those included in Section 2.1.
Final analysis of study data once all patients have discontinued treatment, and all required safety follow-up has been completed or the patient has died, been lost to follow-up or has withdrawn their consent to further participation in the study or the last patient on treatment has been enrolled to a separate protocol, whichever comes first, will include the data with an assessment date or event start date (e.g. vital sign assessment date or start date of an adverse event) prior to or on the cut-off date. For example, if the cut-off date is 30DEC2015, an AE starting on 28DEC2015 will be reported, whereas an adverse event starting on 31DEC2015 will not be reported.

5.2 Patient classification into analysis sets

This section provides additional details to those included in Section 2.2.

Patients are excluded from the analysis populations based on the protocol deviations entered in the database and/or on specific patient classification rules as shown in Table 5-1 below. Only data from patients having signed informed consent are used in the analyses described below.

Table 5-1 Patient classification rules

Analysis Population	Protocol deviation ids leading to exclusion	Additional patient classification rules leading to exclusion
Full Analysis Set	N/A	Patients who did not receive at least one dose of study drug
Safety Set	N/A	Patients who did not receive at least one dose of study drug.
Dose determining Set	N/A	Patient did not received at least 16 of the 21 doses in cycle 1 or did not experience a DLT if receiving less than the prescribed number of doses.
Pharmacokinetic analysis set	N/A	Patients receiving LDK who do not have at least one evaluable PK sample as defined in Section 2.10

5.3 Derivations

Month derivation

For all derivations, a month will be calculated as (365.25 / 12) = 30.4375 days. If duration is to be reported in months, duration in days will be divided by 30.4375.

Dose interruptions and dose changes

This section provides additional details to those included in Section 2.4.

All calculations of dose interruptions and dose changes are based on corresponding CRF check box and the dose actually taken by the patient.

An interruption is defined as a 0 mg dose taken on one or more days. What follows defines how dose interruptions will be counted in the case of multiple dose interruptions.

- If an interruption occurs consecutively for at least two days due to the same reason, then it will be counted only once (*example: If the actual dose on days 1-3 is 750 mg and actual dose on days 4-5 is 0 mg and dose interruption on days 4-5 is due to AE, then the total number of dose interruptions is 1*).
- If an interruption occurs consecutively for at least two days due to different reasons, then it will be counted for each reason (*example: If the actual dose on days 1-3 is 750 mg and actual dose on days 4-5 is 0 mg and dose interruption on day 4 is due to AE and dose interruption on day 5 is due to dosing error, then the total number of dose interruptions is 2*).
- If an interruption occurs for more than one day due to the same reason, but the days are not consecutive , i.e. there is at least one dosing day in between, then each dose interruption will be counted as a different occurrence (*example: if the actual dose on days 1, 3 and 5, is 750 mg and actual dose on days 2 and 4 is 0mg, and dose interruptions on day 2 and 4 are both due to dosing error, the total number of dose interruptions is 2*).

A dose change is defined as a change in dosing from one record to the next; however, a dose interruption will not be counted as a dose change.

Dose reductions are a subset of dose changes where dose changes to higher than protocol-planned dose are excluded.

5.4 Efficacy endpoints

For further details on efficacy endpoints, see Section 14 (Appendix 5 and 6) of the protocol. For the evaluation of tumor-response related endpoints, response is assessed by investigator per RECIST 1.1 and IWG criteria.

Response and progression evaluation will be performed according to the Novartis RECIST 1.1 guidelines and the Novartis Cheson criteria guidelines, included in Section 14 (Appendix 5 and 6) of the LDK378X2103 protocol.

The text below gives more detailed instructions and rules needed for programming of the analyses described in Sections 2.6 and 2.7

5.4.1 Implementation of RECIST and Cheson guidelines

Disease progression

PD should only be assigned if it is confirmed by an objective assessment method. If a new lesion is detected using an objective assessment method other than radiologic scan, it should be entered on the 'New lesion' RECIST and Cheson eCRF with appropriate method (or method='Other').

In particular, discontinuation due to disease progression or death due to progressive disease, without supporting objective evidence (as defined above), will not be considered as PD in the determination of BOR, the derivation of any efficacy endpoint or efficacy analysis.

Change in imaging modality per RECIST 1.1

Per RECIST 1.1, 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.

Change in imaging modality per Cheson

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 an "Unknown" overall radiological response assessment. However, another overall radiological response than the Novartis calculated "Unknown" response might 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.

Determination of missing adequate tumor assessments

For the computation of ORR, patients without any radiological assessment after the start date of study drug will be counted as failure.

Partial or complete responses reported prior to any additional anticancer therapy will be considered for ORR computation irrespective of the number of missed assessments before response. In this section, the 'missing adequate assessment' is defined as assessment not done or assessment with overall lesion response equal to UNK. For the sake of simplicity, the 'missing adequate assessment' will also be referred as 'missing assessment'.

As detailed in Section 14 (Appendix 5 and 6) of the LDK378X2103 protocol, the PFS censoring and event date options depend on the presence and the number of missing tumor assessments. *For example, an event occurring after two or more missing assessments is censored in the analysis of PFS at the last adequate tumor assessment before the event date.*

An exact rule to determine whether there is none, one or two missing assessments is therefore needed. This rule will be based on the distance between the last adequate tumor assessment date and the event date.

If the distance is larger than threshold D_1 or D_2 then the analysis will assume one or two missing assessments, respectively. The threshold D_1 will be defined as the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. Similarly, the threshold D_2 is defined as two times the protocol specified interval between the tumor assessments plus the protocol allowed window around the assessments. For example, n this study, the protocol defined schedule of tumor assessment is every 6 weeks for the first six cycles, and each assessment is expected to be performed at the scheduled time point plus or minus 1 week, i.e. the window is 2 weeks, then any distance larger than $D_1 = 6+2 = 8$ weeks means one missing assessment and any distance larger than $D_2 = (2*6) + 2 = 14$ weeks means two missing assessments. Please see protocol 7.1 for the complete schedules for tumor assessments.
The same definition of D_2 will be used to determine the PFS censoring reason. Possible censoring reasons for PFS are:
1: Ongoing without event
2: Lost to follow-up
3: Withdrew consent
4: Adequate assessment no longer available
5: New cancer therapy added
6: Event after >=2 missing tumor assessments

New cancer therapy used in RECIST calculations include any anti-cancer therapy as recorded in the medication, surgery (diagnostic biopsies are excluded) or radiotherapy CRF pages and includes LDK378 treatment from the extension-treatment phase.

Eligibility per RECIST 1.1 (Non-measurable disease only at baseline)

As specified in Section 14 (Appendix 5) of the LDK378X2103 protocol, the RECIST 1.1 criteria imply that only patients with measurable disease at baseline should be included in the study.

If a patient without measurable disease is enrolled, the intent-to-treat (ITT) principle requires including these patients in the analyses. Hence, analyses will be based on FAS including patients with either measurable or non-measurable disease per RECIST 1.1. Therefore, a rule needs to be specified on how to handle these cases.

As specified in Table 14-8 of Section 14 (Appendix 5) of the LDK378X2103 protocol, overall lesion response can be derived for patients without measurable disease at baseline as follows (Table 5-2).

Table 5-2 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] In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination.

Eligibility per Cheson criteria.

As specified in Section 14 (Appendix 6) of the LDK378X2103 protocol, Cheson criteria imply that only patients with measurable disease should be in included in the study. In particular, patients should have **at least one measurable *nodal* lesions greater than 20mm in the long axis**. In cases where the patient has no measurable nodal lesions greater than 20mm in the long axis at baseline, then the patient must have at least one measurable extranodal lesion (long and short axes are >= 10mm).

Missing baseline tumor assessment

Since the timing of PD cannot be determined for patients with missing baseline tumor assessment, these patients are censored in the PFS analysis at the start date of treatment. This rule, however, only applies to the 'PD component' of the PFS or DOR assessment.

Patients without baseline tumor assessment who die within D_2 distance from start date of treatment will be counted as having an event in the primary analysis of PFS.

5.4.2 Kaplan-Meier estimates

To analyze time to event variables (DOR and PFS) an estimate of the survival function will be constructed using ***Kaplan-Meier (product-limit) method*** as implemented in PROC LIFETEST with METHOD=KM option (see example below). The median time to event and estimated event rates at different time points will be estimated, along with associated 95% two-sided CIs derived based on the complementary log-log transformation. This will be conducted via the SAS procedure LIFETEST. The TIME statement will include a variable with survival times (*survtime* in the example below) and a (right) censoring variable (*censor* in the example below) with a value of 1, representing censoring:

```
PROC LIFETEST data = dataset
   METHOD = KM
   CONFTYPE=LOGLOG;
TIME survtime*censor(1);
RUN;
```

/* *survtime* represents variable containing event/censor times;
censor represents censoring variable (1 = censored, 0 = event); */

Kaplan-Meier survival and failure function estimates from this procedure will be used to construct the Kaplan-Meier figures

Median survival will be obtained along with 2-sided 95% CIs calculated from PROC LIFETEST output using the method of Brookmeyer & Crowley, 1982..

Kaplan-Meier estimates with 2-sided 95% CIs at specific time points will be summarized. The time points can be expressed in weeks or in months depending on the time-to-event variable. The CIs will be constructed using Greenwood's formula [Collet, 1994, p.23] for the standard error of the Kaplan-Meier estimate.

The Kaplan-Meier graphs will be constructed using SAS software.

5.4.3 Confidence interval for response rate

ORR will be summarized in terms of percentage rates with 95% CIs. An exact binomial confidence interval (implemented using SAS procedure FREQ with EXACT statement for one-way tables) will be calculated (Clopper & Pearson,1934).

SAS procedure FREQ will be used to estimate the proportion of responders (binary outcome = 1 or "Yes"), along with the associated 95% (=100 × (1 – *two-sided alpha level*)) two-sided Pearson-Clopper CI for the hypothesis test of the *null proportion* (0.25). These estimates are obtained as follows:

```
proc freq data = dataset;
      table binary event /
            binomial(
                  level = "Yes")
            alpha = two-sided alpha level;
      exact binomial;
```

When there are no responders, SAS does not produce a CI by default. To obtain a CI in this situation, PROC FREQ is used as specified above except changing **level**="No". From the results of this modified procedure, the values in percent of the LCL and UCL of a 0% response rate are calculated as follows:

$$LCL_{LEVEL="Yes"}\ (\%) = 100\% - UCL_{LEVEL="No"}\ (\%)$$

$$UCL_{LEVEL="Yes"}\ (\%) = 100\% - LCL_{LEVEL="No"}\ (\%)$$

5.5 Safety evaluations

The text below gives more detailed instructions and rules needed for programming of the analyses described in Section 2.8

5.5.1 Multiple assessments within post-baseline visits

For all analyses regarding abnormal assessments or analyses based on worst or best post-baseline value (laboratory, ECGs, vital signs, ECOG performance status), all post-baseline values will be included (scheduled, unscheduled, repeat). All unscheduled and repeat measurements will be included in listings.

Laboratory Data

For laboratory data, assessments can be collected from both local and central laboratory on the same date. For shift tables using CTC grades to compare baseline to the worst post-baseline value, the assessment with worst post-baseline value is used for analyses irrespective of the source. For LFT summaries, where concurrent measurements are used in the calculation of number and percentage of patients with worst post-baseline values, the assessment with worst post-baseline value is used (since worst values are based on the largest ratio of lab value to its ULN for each patient) although the worst values for the different parameters may be coming from different laboratories.

ECGs

For all patients, three ECGs are targeted to be measured at the protocol-defined (nominal) time-points. If a patient has more than one measurement at a nominal time point, the average of all available measurements associated with the nominal time point will be used for the analyses.

5.5.2 Baseline

As defined in Section 2.1.1, the last available assessment before or on the date of start of study drug is defined as “baseline” value or “baseline” assessment.

Laboratory data

If both central and local laboratory assessments were performed on the same date and corresponding to the baseline assessment date, then the central laboratory assessment will be used for the calculation of baseline.

ECGs

Baseline for ECG measurement is the average of all available measurements (unscheduled, if applicable) taken prior to dosing on the date associated with the last available ECG measurement before or on the date of start of study treatment. To determine whether ECG measurement was taken prior to dosing, ECG time will be compared with dosing time, if available. Unscheduled assessments will be included in the calculation of the average if ECG time is before dosing time. Study day one scheduled pre-dose ECGs will be considered to have been obtained prior to study drug administration if dosing time or ECG time is missing.

If a scheduled pre-dose measurement actually occurred post-dose, then the corresponding measurement will be treated and analyzed similar to an unscheduled post-dose measurement. For unscheduled assessments on study day 1,

- if dosing time is non-missing, then the assessment is classified as post-baseline if ECG time is later than dosing time.
- if dosing time is missing, the assessment is classified as post-baseline.

The same ECG assessments will be used for both qualitative and quantitative baseline evaluations.

5.5.3 Laboratory Parameters

This section provides further detail on the analysis of laboratory parameters that will be listed and summarized as described in Section 2.8.3 .

Hematology

Hematologic tests include Hemoglobin, platelets, white blood cells (WBC) with differentials (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute)

The following rules will be applied to derive the WBC differential counts when only percentages are available (this is mainly for neutrophils and lymphocytes, because CTC grading is based on the absolute counts).

The method to convert the value is straightforward: for each subject, the original lab value (%) is divided by 100 and multiplied by WBC count e.g. for neutrophils (NEU):

NEU count = (WBC count) * (NEU%value/100)

In order to derive the corresponding absolute normal range, the rule to be applied depends on the availability of the % range and the absolute range for the differential:

- If % absolute range NOT missing (% range is or isn't missing), then use the absolute range provided by the site
- If % range NOT missing and absolute range missing, then the % normal limits (i.e. LLN and ULN) are divided by 100 and multiplied by the corresponding normal limits of WBC count, e.g. for neutrophils NEU):

  LLN for NEU count = (LLN for WBC count)* (LLN for NEU%value /100)

  ULN for NEU count = (ULN for WBC count)*(ULN for NEU%value/100)

Biochemistry

The following calculation will be applied for corrected calcium in SI unit:

Corrected calcium (mmol/L) =measured total Ca (mmol/L)+0.02 (40-serum albumin[g/L]), where 40 represents the average albumin level in g/L.

5.6 Handling of missing or partial dates

For patients not known to have died prior to the cut-off date:

- All events with start date before or on the cut-off date, and with end date missing or after the cut-off date, or after the date of withdrawal of informed consent, will be reported as "continuing".
- This approach applies, in particular, to AEs and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings.

If imputation of an end date is required for a specific analysis (e.g. for a dose administration record with missing end date or last date of study drug after the cut-off date), the end date will be imputed to the min(cut-off date, death date and withdrawal of informed consent date)for the purpose of calculating duration of exposure to study drug and dose intensity. The imputed date will be displayed and flagged in the listings.

5.6.1 AE date imputation

Date imputation is the creation of a new, complete date from a partial one according to an agreed and acceptable algorithm. Missing date for AE will be handled according to rules specified below. A partial date is simply an incomplete date e.g. DDOCT2001: the days are missing from this DDMMMYYYY date.

Partial AE start dates, if left partial, would ultimately mean the following

It would not be possible to place the AE in time.

Therefore, the treatment/dosage at the time of the event would be unknown.

Therefore, the event could not be reported/summarized appropriately – if at all.

Therefore, it is important to perform date imputation to ensure that as many data events are represented as correctly as possible. Of course partial and/or missing dates should *also* be caught as edit checks and passed back to the investigator for resolution.

There **will be no** attempt to impute the following:

- **Missing** AE start dates
- AE start dates **missing the year**
- Partial/missing AE **end dates**

The following Table 5-4 explains the abbreviations used.

Table 5-3 AE/treatment date abbreviations

	Day	Month	Year
Partial Adverse Event Start Date	<not used>	AEM	AEY
Treatment Start Date (TRTSTD)	<not used>	TRTM	TRTY

The following matrix Table 5-5 describes the possible combinations and their associated imputations. In the light grey boxes, the upper text indicates the imputation and the lower text the relationship of the AE start date to the treatment start date (TRTSTD).

Table 5-4 AE partial date imputation algorithm

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
AEY MISSING	NC Uncertain (D)	NC Uncertain (C)	NC Uncertain (C)	NC Uncertain (C)
AEY < TRTY	Before TRTSTD (B)	Before TRTSTD (C)	Before TRTSTD (B)	Before TRTSTD (A)
AEY = TRTY	Uncertain (E)	Before TRTSTD (A)	Uncertain (A)	After TRTSTD (A)
AEY > TRTY				

	AEM MISSING	AEM < TRTM	AEM = TRTM	AEM > TRTM
	After TRTSTD	After TRTSTD	After TRTSTD	After TRTSTD

The following Table 5-6 is the legend to the above table.

Table 5-5 AE/treatment date relationship and imputation legend

Relationship	
Before TRTSTD	Indicates AE start date prior to Treatment Start Date
After TRTSTD	Indicates AE start date after Treatment Start Date
Uncertain	Insufficient to determine the relationship of AE start date to Treatment Start Date
Imputation Calculation	
NC / Blank	No convention/imputation
(A)	01MONYYYY
(B)	TRTSTD+1
(C)	15MONYYYY
(D)	01JULYYYY
(E)	01JANYYYY

The following Table 5-7 gives a few examples.

Table 5-6 AE imputation example scenarios

Partial AE start date	Treatment start date	Relationship	Imputation Calculation	Imputed Date
12mmyyyy	20OCT2001	Uncertain	NC	<blank>
ddmmm2000	20OCT2001	Before	(D)	01JUL2000
ddmmm2002	20OCT2001	After	(E)	01JAN2002
ddmmm2001	20OCT2001	Uncertain	(B)	21OCT2001
ddSEP2001	20OCT2001	Before	(C)	15SEP2001
ddOCT2001	20OCT2001	Uncertain	(B)	21OCT2001
ddNOV2001	20OCT2001	After	(A)	01NOV2001

5.6.2 Concomitant medication date imputation

The imputation of the start date of concomitant medication will follow the same conventions as for AE date. Partial concomitant medication end dates will not be imputed.

5.6.3 Incomplete date of initial diagnosis of cancer and date of most recent recurrence

Missing day is defaulted to the 15th of the month and missing month and day is defaulted to 01-Jan.

5.6.4 Incomplete date for anti-neoplastic therapies

Prior therapies

Start date:

The same rule which is applied to the imputation of AE/concomitant medication start date will be used with the exception that for scenario (B) will be replaced to be 'start date of study drug -1'.

End date:

Imputed date = min (start date of study drug, last day of the month), if day is missing;

Imputed date = min (start date of study drug, 31DEC), if month and day are missing.

If the end date is not missing and the imputed start date is after the end date, use the end date as the imputed start date.

If both the start date and the end date are imputed and if the imputed start date is after the imputed end date, use the imputed end date as the imputation for the start date.

Post therapies

Start date:

Imputed date = max (last date of study drug + 1, first day of the month), if day is missing;

Imputed date = max (last date of study drug + 1, 01JAN), if day and month are missing.

End date: No imputation.

5.6.5 Incomplete assessment dates for tumor assessment

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, the incomplete date(s) are not considered for calculation of the assessment date and assessment date is calculated as the latest of all investigation 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 PD, the assessment date is calculated as the earliest date of all investigation dates at that evaluation number. If all measurement dates have no day recorded, the first 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 the previous and the following assessment. If both a previous and following assessments are not available, this assessment will not be used for any calculations. In case of multiple imaging scans performed within an evaluation, if some imaging dates for tumor assessment under the same evaluation for a patient are before as well as after cut-off, the entire evaluation will not be included for analyses based on the pre-specified

cut-off. Hence, only complete tumor assessments (with all imaging dates on or prior to the cut-off) for an evaluation will be included for analyses as determined by the pre-specified cut-off.

5.6.6 Incomplete date for death

All dates must be completed with day, month and year.

Missing month and year will not be imputed. If the day is missing, death will be imputed to the maximum of the full (non-imputed) last contact date (excluding the date of death) and the following:

- Missing day: 1st day of the month and year of death

5.6.7 Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the last complete date among the following:

Table 5-8 Last contact date data sources

Source data	Conditions
Date of Randomization	No Condition
Last contact date/last date patient was known to be alive from Survival Follow-up page	- Patient status is reported to be alive, lost to follow-up or unknown.
Start/End dates from further antineoplastic therapy	Non-missing medication/procedure term.
Start/End* dates from drug administration record	Non-missing dose. Doses of 0 are allowed.
End of treatment date from end of treatment page	No condition.
- Tumor (RECIST) assessment date - For non-RECIST studies, any specific efficacy assessment date if available	Evaluation is marked as 'done'.
Laboratory/PK collection dates	Sample collection marked as 'done'.
Vital signs date	At least one non-missing parameter value
Performance Status date	Non-missing performance status
Start/End dates of AE	Non-missing verbatim term

- The last contact date is defined as the latest complete date from the above list on or before the data cut-off date . The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used. Completely imputed dates (e.g. the analysis cut-off date programmatically imputed to replace the missing end date of a dose administration record) will not be used to derive the

last contact date. Partial date imputation is allowed for event (death)/censoring is coming from 'Survival information' eCRF.

5.6.8 Incomplete dates for last dose of study drug

Scenario 1

If the last date of study drug is after the cut-off date or is completely missing and there is no end of treatment eCRF page and no death date the patient should be considered to be on-going and use the cutoff date for the analysis as the last dosing date

Scenario 2

If the last date of study drug is completely or partially missing and there is EITHER an end of treatment eCRF page OR a death date available then imputed last dose date:

= 31DECYYYY, if only Year is available and Year < Year of min (EOT date, death date)

= Last day of the month, if both Year and Month are available, and EITHER:

-- Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date) OR,

-- Year < Year of min (EOT date, death date) irrespective of the month

= min (EOT date, death date), for all other cases

5.6.9 Incomplete dates for disease progression prior to start of study drug

If day of PD associated with prior antineoplastic medication is missing then imputed PD date:
= min (midpoint between the end date of the prior antineoplastic medication and the end of the month, start date of LDK, start date of prior medication from the next regimen), if end date of prior antineoplastic medication is in the same month as the PD date,
= min (15th of the month of the PD date, start date of LDK, start date of prior medication from the next regimen), if end date of prior antineoplastic medication is in a month prior to the PD date
= 15th of the month of the PD date, if end date of prior antineoplastic medication is in a month after the PD date.
If both day and month of PD associated with prior antineoplastic medication are missing then imputed PD date:
= min (midpoint between the end date of the prior antineoplastic medication and the end of the year, start date of LDK, start date of prior medication from the next regimen), if end date of prior antineoplastic medication is in the same year as the PD date
= min (July 1 of the year of the PD date, start date of LDK, start date of prior medication from the next regimen), if end date of prior antineoplastic medication is in a year prior to the PD date
= July 1 of the year of the PD date, if end date of prior antineoplastic medication is in a year after the PD date
Completely missing PD dates will not be imputed. The start date of medication from the next regimen is based on the earliest start date of any medication(s) from the next regimen. For the mid-point calculation, if odd days in between, (e.g. last dose of medication is 27 June 2012,

and end of the month is 30 June 2012), then use the next day from the midpoint calculation (e.g. mid-point is 29 June 2012).

5.7 PK analyses

The text below gives more detailed instructions and rules needed for programming of the analyses described in Section 2.10.

The random effects model with patient as random effect will be used to estimate the intra-patient and inter-patient variation. The following SAS code will be used:

PROC MIXED data = *pkdataset*;

CLASS *patient*;

MODEL *Log_ Ctrough* = / solution;

RANDOM *patient;*

RUN;

/* *log_Ctrough* refers to log transformed SS Ctrough concentration */

The inter-patient CV% for SS Ctrough will be calculated as:

CV% = sqrt(exp(variance estimate for random patient effect from SS Ctrough model) –1)×100

The intra-patient CV% for SS Ctrough will be calculated as:

CV% = sqrt(exp(residual variance from SS Ctrough model) – 1)×100

6 Reference

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