NOVARTIS

Clinical Development

LDK378

CLDK378A2109 / NCT02040870

A phase I/II multicenter, open-label, single-arm study of LDK378, administered orally in adult Chinese patients with ALK-rearranged (ALK-positive) advanced non-small cell lung cancer (NSCLC) previously treated with crizotinib

Statistical Analysis Plan (SAP)

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Document History – Changes compared to previous version of RAP module 3.

Version	Date	Changes
V2.0	05-Jun-2014	Final version 2.0
Amendment 1	17-Dec-2014	The content and language of this RAP document were modified to align with protocol amendment 1 and to align with the analyses implemented in other LDK378 studies. Further details are described below: Section 2.4: [redacted] Figure 1.1: Number updated to reflect the sample size change. Section 3.1.1.6 Derivation rules for baseline (including ECG) were further clarified. Section 3.1.2: Updated timing primary CSR analysis to be after all patients completed 24 weeks (6 cycles) of treatment. Section 3.1.3: "Efficacy analysis set" definitions were added for the efficacy population used for interim analysis. A new major PD "Patient has been previously treated with more than 2 lines of chemotherapy" was added. Added criteria that patient should take study drug according to the original assigned dose for at least 5 consecutive days without interruption or dose modification prior to the PK sampling day (except for PK run-in Day 1 for patients with extensive assessment) for evaluable full PK profile Section 3.1.4 Table of patients classification rules are added. Section 3.2.2 & Section 3.2.6: Version information added to MedDRA and WHO drug dictionary.

Version	Date	Changes
		Section 3.2.8: Clarification added for pharmacokinetic analysis using PAS. [redacted] CLss/F is added as a secondary parameter for PK analysis. Section 3.2.9.1, Section 3.2.8: Minor changes to adverse event section to align with protocol amendment 01 and LDK378 program. Section 3.2.9.2 The wording for the derivation of CTC grading for laboratory values was clarified and corrected to cover cases such as creatinine increased grading when the post-baseline value is ≤ULN Section 3.2.9.4. Added shift tables for ECOG status from baseline to best post baseline. Section 3.3: [redacted] Section 3.4: Confidence interval provided for the larger sample size. Section 4.1.1: This section is removed as this RAP now is in alignment with the new updated protocol. Section 4.2.2: Source of ORR derived based on the raw data per investigator was removed. This source is used only for data cleaning purposes. Section 4.3: Categories to describe whether the questionnaire was completed were updated to align with CRF. Section 4.4: More details and clarification added for PK analyses.

Version	Date	Changes
		Appendix 1: Tables/Listings on concomitant medications and significant non drug therapies were split into separate listings as per NCDS. The list of output for IA was updated.
Amendment 2	18-Jan-2016	Naming conventions have been updated for some outputs to align with LDK378 program. Section 2.4: • Updates in study design section to remove "start of a new anti-cancer therapy" from the list of allowable reasons to stop collection of tumor assessments to align with protocol amendment 2. Section 3.1 • The major inclusion/exclusion criteria leading to exclusion from PPS were updated in 3.1.3 per team discussion; the classification rules in section 3.1.4 were updated and further clarified. Section 3.2 • Listing of ALK status in section 3.2.2 was removed as the same has been mentioned in the [redacted] • Updates in the PK parameter table to align with protocol v03. • Additional AE summaries were added and the list of AESI's was updated in Sec 3.2.9.1. • The list of laboratory values to be summarized was updated in section 3.2.9.2. • Denominator for new abnormality post baseline ECGs were clarified in Section 3.2.9.3. The interval to define "lost to follow up" for overall survival was updated to 18 weeks per LDK phase II practice. • [redacted] • Section 4.1:Clarification on the handling of missing date in section 4.1.2. Section 4.2

Version	Date	Changes
		• Clarified that change in contrast use in conventional or spiral CT is not considered a change in modality in Sec 4.2.1. • The language on PFS censoring rules was updated in Sec 4.7.1. • Updated the guidelines for the display of the waterfall graph in Sec 4.2.1. Section 4.4 • Specified the calculation of inter-patient CV% for SS Ctrough. Section 4.5 • List of output for FIR updated
Addendum 1	03-Mar-2016	Section 3.2.10 • The definition of disease control rate (DCR) was updated as the proportion of patients with best overall response of CR, PR, SD, or Non-CR/Non-PD. Patients with a best overall response of Non-CR/Non-PD will also be included in the numerator for DCR calculation.
Amendment 3	03-Jan-2017	Section 3.2.10.2 – Progression free survival Added two extra summary tables of PFS by brain metastasis at baseline status for SCE Section 3.2.10.2 – Overall intracranial response rate Added definition and summary table of OIRR with measurable/non-measurable brain metastases Section 4.1.6 Added the calculation rules for dose interruptions and dose changes in details
Amendment 4	13-Feb-2017	Section 3.2.9.1 – Safety evaluation Added two AE tables for safety disclosure in EudraCT and CT.gov. [redacted]

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1 Introduction

1.1 Document content

This Statistical Analysis Plan (SAP) describes the planned statistical analysis methods for the final clinical study report of LDK378A2109. It is structured as

- a draft of Section 9.7 (Statistical methods planned in the protocol and determination of sample size) of the clinical study report (CSR)
- and also a draft of Appendix 16.1.9 (Documentation of statistical methods) of the CSR.

Appendix 16.1.9 text will contain details of statistical methods and issues that are more detailed than would be included in the CSR text. It is written in the future tense. It will be reviewed and updated (including conversion to past tense) for entry into the clinical study report after the analysis has taken place.

The detailed statistical methodology is similar to the RAP module 3 addendum 2 for the primary clinical study report (CSR) which is stored in the CREDI folder: *CREDI Projects/L/LDK378/CREDI Studies/LDKA2109/Administrative Files (study level)/RAP or RAMP Meeting*, except for the changes noted in the document history.

1.2 References

The following documents are used or referred to for the RAP generation:

- Clinical Trial Protocol CLDK378A2109 amendment version 03 (07Oct, 2015)
- Casebook CLDK378A2109 version 02 (05Aug, 2015)

2 Study objectives and study design

2.1 Primary objectives

- To characterize the pharmacokinetics of LDK378 in Chinese adult patients with ALK-rearranged NSCLC previously treated with crizotinib following single and multiple daily oral doses of LDK378.
- To assess the safety and tolerability of LDK378 after continuous 750 mg once daily dose in Chinese adult patients with ALK-rearranged NSCLC.

2.2 Secondary objectives

2.2.1 Key secondary objective

- To demonstrate the antitumor activity of LDK378, as measured by overall response rate (ORR) to LDK378 by investigator assessment.

2.2.2 Other secondary objectives

To evaluate response related endpoints as assessed by the investigators per RECIST 1.1:

- Duration of response (DOR)

- Disease control rate (DCR)
- Time to Response (TTR)
- Overall intracranial response rate (OIRR)
- Progression-free survival (PFS)
- Overall survival (OS)

ORR and OIRR will also be evaluated as assessed by Blind Independent Review Committee (BIRC).

2.4 Study design

This is a phase I/II, open-label, multi-center study to assess the PK, safety, tolerability and efficacy of LDK378 in adult Chinese patients with locally advanced or metastatic NSCLC harboring a confirmed ALK rearrangement. Patients must have demonstrated progression during or after crizotinib treatment whether or not previously treated with cytotoxic chemotherapy and have no available ALK-targeted treatment options.

Overall approximately 100 patients will be enrolled in the study. The first 15 enrolled patients will enter a 5-day PK run-in period during the phase I component of this study. They will have PK sampling over 120-hour during the run-in period following a single oral dose at 750 mg. Additional patients may be enrolled in the study with the 5-day PK run-in period in case PK profiles from some of the enrolled patients are deemed not evaluable

The phase II component of the study will start on Cycle 1 Day 1 for all enrolled patients. During this period LDK378 will be given as continuous daily oral dosing at 750 mg QD in 28 -day cycles.

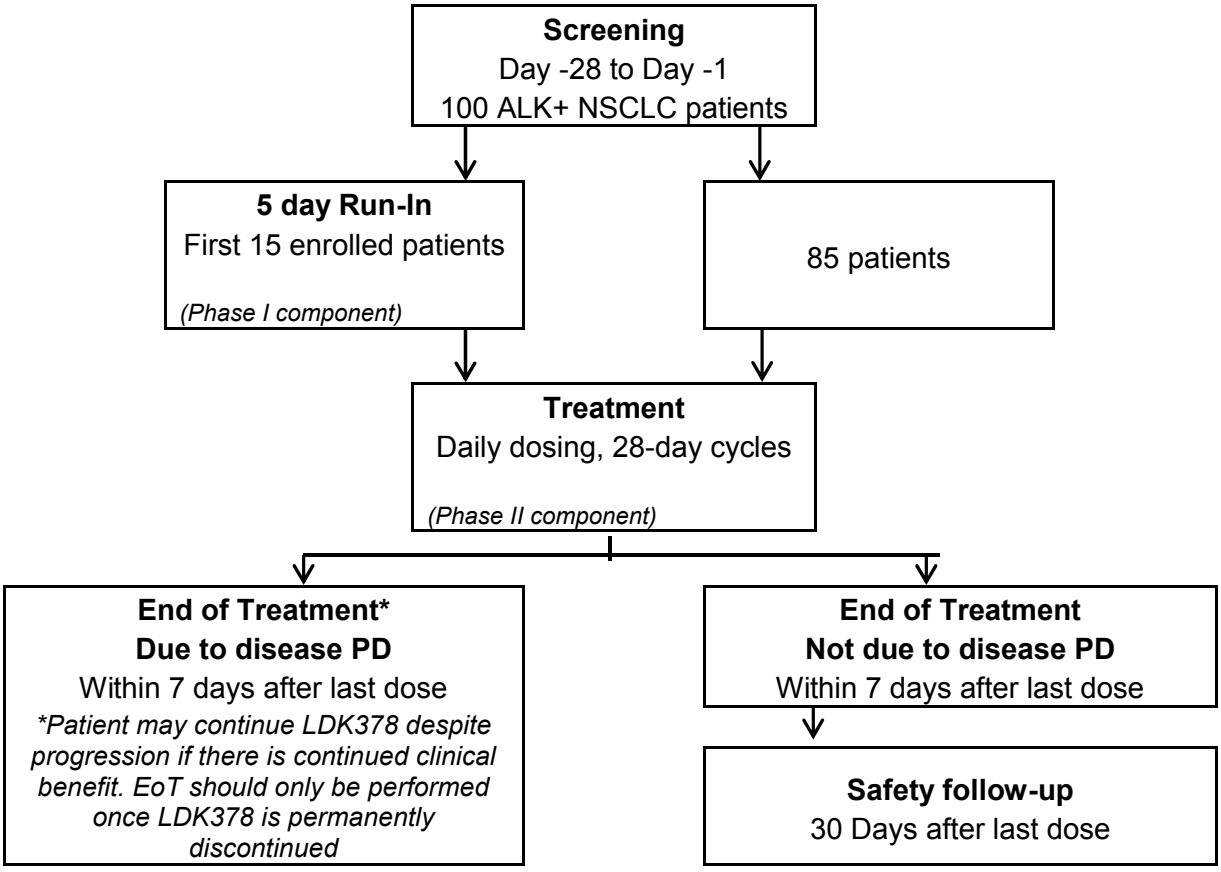
Extensive PK assessment will be collected for the first 15 enrolled patients to obtain approximately 12 evaluable full profiles. Sparse PK samples will be collected for the rest of patients. Adverse events will be collected at every visit after informed consent obtained. Laboratory assessment including hematology and blood chemistry will be taken at screening, run-in Day 1 for the first 15 enrolled patients, Day 1, Day 8, Day 15 for cycle 1 and Day 1 for subsequent cycles. Separate ECG monitoring schedules will also be collected for patients with extensive PK assessment and those with sparse assessment.

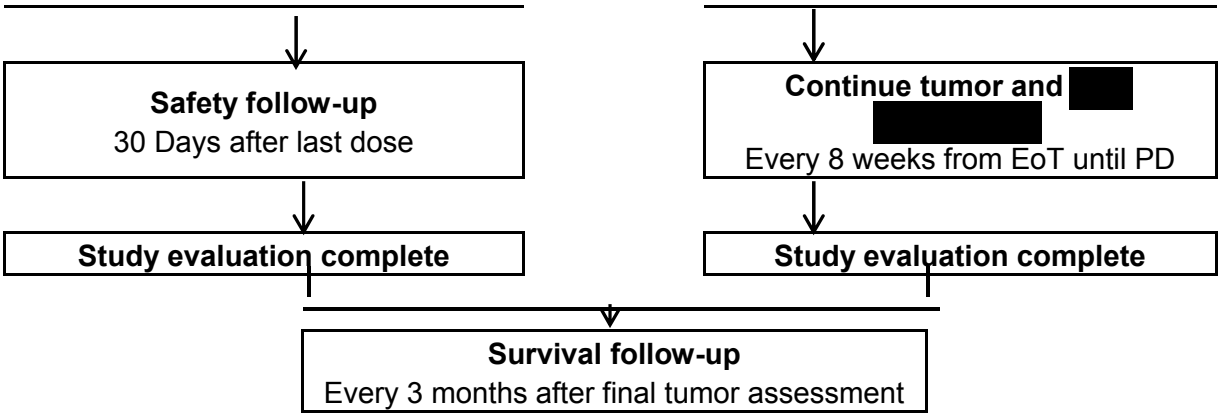
Tumor response will be evaluated every 8 weeks (i.e. every 2 cycles) starting from the first day of treatment with LDK378 until the time of RECIST-defined Progressive disease (PD) by investigator assessment, withdrawal of consent for further follow-up, loss to follow-up or death. This schedule of tumor assessment will continue regardless of dose interruptions. For patients who discontinue treatment in the absence of progression, tumor assessments will continue every 8 weeks until progression of disease, withdrawal of consent for further follow-up, loss to follow-up or death.

Treatment with LDK378 will continue until the patient experiences a RECIST-defined PD on LDK378 as assessed by the investigator, an unacceptable toxicity that precludes further treatment, discontinues treatment at the discretion of the patient or investigator, starts a new anti-cancer therapy or dies. Please refer to Figure 1-1 for flow chart of the study design.

If the patient experiences RECIST-defined progressive disease (PD), treatment with the study drug may be continued if, in the judgment of the investigator, there is still evidence of clinical benefit. When the patient discontinues from study treatment an End of Treatment (EOT) visit must be performed within 7 days of the last dose of LDK378. Patients will be contacted for the safety follow-up 30 days after their last dose of LDK378. Following the cessation of tumor follow-up assessments, patients will be contacted every 3 months to determine survival status and/or whether the patient started any other antineoplastic therapies since discontinuing study treatment.

Figure 2-1 Study design





2.5 Study flow and visit schedule

See Table 7-1 in the protocol.

3 Draft of Section 9.7 of CSR - Statistical methods planned in the protocol and determination of sample size

3.1 Draft of Section 9.7.1 of CSR - Statistical and analytical plans

3.1.1 Definitions

3.1.1.1 Study drug and study treatment

Study drug and study treatment both refer to LDK378 and will be used interchangeably.

3.1.1.2 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 is administered and recorded on the Dosage Administration Record (DAR) electronic Case Report Form (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 is administered and recorded on the DAR eCRF. This date is also referred as last date of study drug.

3.1.1.3 Duration of exposure and Intensity

Definitions of duration of exposure, cumulative dose, average daily dose, actual dose intensity (DI), planned dose intensity (PDI), relative dose intensity (RDI), 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
- Average daily dose (mg/day): cumulative dose (mg)／number of dosing days, drug free day(s) in PK run-in period are not counted
- DI (mg/day): cumulative dose (mg)／duration of exposure (days)
- PDI (mg/day): cumulative planned dose (mg) / duration of exposure (days)
- RDI (%): 100 × DI (mg/day)／PDI (mg/day)

The cumulative planned dose is defined as the total planned dose according to the planned dosing schedule during the study treatment exposure. It is therefore calculated as follows: cumulative planned dose (mg) = protocol planned dose of 750 (mg)* duration of exposure.

For the first 15 patients who are planned to receive a single dose during the PK run-in period (of 5 days), and patients receive daily dosing thereafter, the cumulative planned dose is calculated as follows:

Cumulative planned dose (mg) =

- 750 (mg) * (duration of exposure -4), if duration of exposure (day) >5
- 750 (mg), if duration of exposure (day) ⩽5

The similar procedure for calculation is applied to calculation of dosing days for the first 15 patients enrolled in the PK run-in period;

Number of dosing days (days) =

- duration of exposure – (number of zero dose days + 4), if duration of exposure (day) >5
- duration of exposure, if duration of exposure (day) ⩽5

3.1.1.4 Dose interruption and dose change

Dose interruption and dose change will be listed and summarized as reported in the DAR eCRF.

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

3.1.1.5 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) will be calculated using the start date of study drug as the origin. This also applies to patients who received single dose at PK run-in period. For assessments occurring after or on the start date of study drug, study day will be calculated as:

Study Day =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 = Event date - start date of study drug.

The study day will be displayed in the data listings.

3.1.1.6 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. For cases when the assessment is planned to be performed before the first dose of study drug and the assessment is performed on the same day as the first administration of study drug:

- If either the assessment or first dose time point is not collected or is missing, it will be assumed that the assessment was performed prior to study drug administration.
- If both assessment and first dose time points 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 unless otherwise specified. 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 (or PK run-in 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.

Laboratory data

If both central and local laboratory assessments are 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 each ECG measurement is the average of the pre-dose replicate measurements on the baseline day. Unscheduled assessments will not be included in the calculation of the average. Study day 1 (PK run-in day 1 for the first 15 patients and Cycle 1 day 1 for the rest patients) 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 the same as an unscheduled post-dose measurement. For unscheduled assessments on study day 1, if dosing time is non-missing, then the assessment is considered as post-baseline if ECG collection time is later than dosing time. If dosing time is missing, these unscheduled assessments will be considered as post-baseline.

3.1.2 Data included in analyses before the completion of the study

An interim analysis will be performed after the first 30 patients enrolled have completed at least 4 cycles of treatment with LDK378 or have discontinued earlier. For the interim analysis, all data from patients on or before the interim analysis cut-off date will be used.

The primary CSR will be produced after all patients have undergone at least 24 weeks (6 cycles) of treatment with LDK378 or have discontinued earlier. All available data from all patients up to this cutoff date will be analyzed. Only 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 will

be included in each analysis. (Example: If the cut-off date is e.g. 15-Oct-2011, an AE starting on 13-Oct-2011 will be reported, whereas an AE with a start date on 17-Oct-2011 will not be reported).

3.1.3 Analysis sets

A patient is considered to be enrolled into the study if they have signed the 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) consists of all patients who receive at least one dose of LDK378. Unless otherwise specified the FAS will be the analysis set used for all analyses and listings.

Efficacy Analysis Set (Interim analysis only)

The Efficacy Analysis Set (EAS) is used in the interim analysis for the analysis of tumor response data based on investigator assessments. It is a subset of the FAS, and consists of patients who received the first dose of LDK378 at least 16 weeks prior to the analysis cutoff date. The EAS will be the primary data set used in interim analysis for the analysis of tumor response data (ORR and DOR based on investigator assessments).

Safety Set

The Safety Set consists of all patients who receive at least one dose of LDK378. All safety data will be analyzed using the Safety Set.

The FAS and Safety Set in this study are identical.

Per-Protocol Set

The Per-Protocol Set (PPS) will consist of a subset of patients in the FAS who are compliant with requirements of the Clinical Study Protocol (CSP). The PPS consists of patients who have an adequate tumor assessment at baseline, a follow-up tumor assessment >7 weeks after starting treatment (unless disease progression is observed per investigator's assessment before that time), and no major protocol deviations. PPS will be used in the supportive analysis of ORR.

The major protocol deviations that will lead to removal of patients from the PPS are listed below:

- No confirmation of ALK positive status by the Abbott Molecular Inc FDA-approved FISH assay or by the CFDA approved IHC Ventana test prior to first dose. Patient has a histologically or cytologically confirmed diagnosis of NSCLC that is not ALK positive as assessed by the Abbott Molecular Inc FDA-approved FISH assay or by the CFDA approved IHC Ventana test.
- No histological or cytological diagnosis of NSCLC
- Neither Stage IIIB nor IV NSCLC
- WHO performance status equal to 3 or 4 at screening

- No prior treatment with crizotinib
- Prior treatment with crizotinib with no noted PD during or after crizotinib treatment OR prior treatment with crizotinib discontinued due to toxicity
- Patient has been previously treated with more than 2 lines of chemotherapy prior to study entry
- No documentation of disease progression at study enrollment
- No measurable lesion from RECIST 1.1 evaluation at baseline per investigator assessment. For analysis by BIRC assessment based on PPS, 'No measurable lesion at baseline' is based on BIRC assessment per RECIST 1.1.
- RECIST lesions previously been irradiated has been chosen as target lesions without a clear progression since irradiation
- Patient has received an ALK inhibitor investigational agent (except Crizotinib) before first dose of study treatment.
- Patient has a history of carcinomatous meningitis
- Patient with symptomatic central nervous system (CNS) metastases neurologically unstable or has required increasing doses of steroids within the 2 weeks prior to study entry.

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 PK sample.

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

A sparse PK sample is considered to be evaluable if:

- The patient takes study drug according to the original assigned dose for at least 5 consecutive days without interruption or dose modification prior to the PK sampling day (except for PK run-in Day 1 for patients with extensive assessment and Cycle 1 Day 1), AND
- On the PK collection day, the patient takes study drug according to the originally assigned dose,
- Vomiting doesn't occur within 6 hours following the last dose intake prior to the PK sample draw, AND
- For the pre-dose sample, draw occurs between 18 to 30 hours after the last dose intake (except for PK run-in Day 1 for patients with extensive assessment and Cycle 1 Day 1), and
- For the pre-dose sample, the draw occurs before the next dose intake, and
- A sample can be considered to be not evaluable as per scientific judgment of the clinical pharmacology expert

An evaluable full PK profile is defined as:

- The patient takes study drug according to the original assigned dose for at least 5 consecutive days without interruption or dose modification prior to the PK sampling day (except for PK run-in Day 1 for patients with extensive assessment and Cycle 1 Day1), AND
- No vomiting occurs within 6 hours following the last dose intake prior to the PK sample draw, AND
- On the PK collection day, the patient takes study drug according to the originally assigned dose, 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 in the merged PK datasets.

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.

3.1.4 Classification into Analysis Sets

Patients were excluded from the analysis populations defined above based on the protocol deviations entered in the database and/or on specific subject classification rules, see Table 3-1 below.

Table 3-1 Patient classification rules

Analysis Population	Patient classification rules leading to exclusion
Full Analysis Set	Patients who did not receive at least one dose of study drug
Efficacy Analysis Set (Interim analysis only)	Patient did not receive at least one dose of LDK378 OR First dose of LDK378 < 16 weeks prior to data cut-off
Safety Set	Patients who did not receive at least one dose of study drug.
Per Protocol Set	Protocol deviations that will lead to removal of patients from Per Protocol Set, i.e. INCL01, INCL02, INCL03, INCL04, INCL07, INCL08, INCL09, INCL10, INCL11, INCL12, INCL13, INCL33，EXCL02, EXCL03, EXCL04 Patient who do not have an adequate tumor assessment at baseline, or a follow-up tumor assessment > 7 weeks after starting treatment (unless disease progression is observed before that time). For PPS (inv.) patients with no target lesions at baseline per investigator are excluded; for PPS (BIRC) patients with no target lesions at baseline per BIRC are excluded.
Pharmacokinetic analysis set	Patients who do not have at least one evaluable PK sample

All protocol deviations and subject classification rules will be finalized before database lock.

Below lists handling of some special cases in analysis set classification:

- If informed consent is not properly obtained from the patient (signed and dated prior to any study related procedures), data from the patient will be excluded from all analysis populations including table summaries and listings.
- If a patient withdraws consent (based on 'Was informed consent withdrawn' is 'Yes' for study informed consent in the "Withdrawal of informed consent" page)
  - If consent withdrawal date is before start of treatment date, or start of treatment date is missing, then patients' data will not be included into any analysis.
  - If consent withdrawal date is after start of treatment date, then all data collected before withdrawal will be included in the analysis, and data collected after consent withdrawal will be excluded from the date of withdrawal by programming cut-off.
- If a patient does not meet inclusion/exclusion criteria:
  - If patient is not treated, then the patient data will be listed in screening failures (see section 3.2.2)
  - If patient is treated, then the patient data will be included in FAS and safety set, but might be excluded from PPS depending on whether this violation is a major protocol deviation or not.

3.1.5 General statistical methodology

3.1.5.1 Multiple assessments within post-baseline visits

If there are multiple measurements/samples within the same post-baseline visit, the last measurement/sample within the visit (sorted by date and as available by time or repeat measurements) will be used in the analysis by visit or overall. For any analyses regarding abnormal assessments or analyses based on worst (or best in the case of ECOG status) post-baseline value (laboratory, ECGs, vital signs, ECOG performance status), all post-baseline values will be included (scheduled, unscheduled, repeat). For any other analyses, only scheduled visits will be included. 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 Common Terminology Criteria (CTC) v4.03 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 Liver function test (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.

12-lead ECG assessments

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

3.1.5.2 Center pooling

Center effects will not be analyzed and the main analyses will therefore be conducted with the pooled datasets.

3.2 Statistical methods used in reporting

3.2.1 General presentation of descriptive summaries

Qualitative data (e.g., sex, race, etc.) will be summarized by frequency count and percentages. Percentages are calculated using the number of patients in the relevant population as the denominator.

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

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

3.2.2 Patient 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. Categorical data (e.g. sex, age groups: <65 and ≥65 years, race, ethnicity, WHO performance status, smoking history) will be summarized by frequency counts and percentages. Continuous data (e.g. age, weight, height, and Body Mass Index (BMI)) will be summarized by descriptive statistics. Height is collected only once in the study. Baseline weight is the last non-missing value observed before the first administration of study drug. BMI will be calculated using height and baseline weight:

$$\text{BMI } (kg/m^2) = \text{weight } [kg] / (\text{height } [m])^2$$

Patient demographic characteristics will be summarized by quartile of average SS Ctrough using Pharmacokinetic Analysis Set (see Section 3.2.8)

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, details of tumor histology/cytology, histological grade, stage at initial diagnosis, stage at time of study entry, time (in months) since initial diagnosis of primary site, time (in

months) from initial diagnosis to first recurrence/progression, time (in months) since most recent relapse/progression, current extent of disease (metastatic sites), number of metastatic sites at baseline, types of lesions (target and non-target lesions) at baseline, number of target lesions at baseline, and disease burden at baseline for target lesion (based on the data collected on the RECIST eCRF page).

Medical history

Medical history and ongoing 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 latest Medical Dictionary for Regulatory Activities (MedDRA) terminology prior to database lock.

Prior anti-cancer therapy

Prior anti-neoplastic (anti-cancer) therapy will be listed in three separate categories: 1. medications, 2. radiotherapy, and 3. 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.

All patients must have received crizotinib for inclusion in the study; reason for crizotinib discontinuation, best response on crizotinib, duration of best response, and time from start of last crizotinib treatment to progression (date of progression on crizotinib - start date of last crizotinib + 1) will be summarized.

Prior anti-neoplastic medications will be summarized by chemotherapy (medication) setting, other therapy (medication) setting, number of prior regimens of chemotherapy. Prior antineoplastic medications will also be summarized by Anatomical Therapeutic Chemical (ATC) class and PT using the latest WHO drug dictionary prior to database lock.

The summary of prior anti-neoplastic radiotherapy will include a summary of radiotherapy locations and settings at last radiotherapy.

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

Screening phase disposition

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screening failure. These patients are not treated with study drug. Frequency counts and percentages will be tabulated for all patients as follows:

- Number (%) of patients who completed screening phase (based on the presence of study phase completion date/ “subject status” is checked as “completed” and the ‘Next phase entered’ is ‘Treatment’ or ‘Treatment run-in’ in the ‘Screening Phase Disposition’ page);
- Number (%) of patients who discontinued during screening phase (based on the presence of date of discontinuation and discontinuation / “subject status” reason entered and ‘Will the subject continue into the next phase of the trial’ is ‘No’ in the ‘Screening Phase Disposition’ page);

- Reasons for screening phase discontinuation (based on reasons recorded in Screening Phase Disposition' page)

All screen failure patients with reasons for screen failure will be listed and summarized by criteria.

3.2.3 Protocol deviations

Frequency counts and percentages of patients in the FAS with any CSR-reportable protocol deviations (related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be tabulated by the deviation category. Major protocol deviations will be tabulated separately.

All protocol deviations will be listed.

3.2.4 Patient disposition

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

Relating to treatment phase:

- Number (%) of patients entered "Treatment run-in" (PK run-in) phase
- Number (%) of patients entered "Treatment" phase
- Number (%) of patients who are still on treatment (based on the absence of the 'End of Treatment Phase Disposition' page);
- Number (%) of patients who discontinued treatment (based on completion of the 'End of Treatment Phase Disposition' page with date of discontinuation and reason of discontinuation/ 'Subject Status' entered);
- Number (%) of patients who entered post-treatment follow-up phase from treatment phase (based on 'Next Phase Entered' is 'Post-treatment follow-up' on the 'End of Treatment Phase Disposition' page for patients who discontinued treatment);
- Number (%) of patients who entered survival follow-up from treatment phase (based on 'Will subject continue into the next phase of the trial' is 'No' and 'Will the subject be followed for survival' is 'Yes' on the 'End of Treatment Phase Disposition' page for patients who discontinued the treatment);
- Number (%) of patients who discontinued from study from treatment phase (based on 'Will subject continue into the next phase of the trial' is 'No' and 'Will the subject be followed for survival' is 'No' on the 'End of Treatment Phase Disposition' page for patients who discontinued the treatment);
- Primary reasons for treatment discontinuation (based on discontinuation reasons entered under 'Subject Status' in the 'End of Treatment Phase Disposition' page);

Relating to the post-treatment follow-up phase:

- Number (%) of patients who are still in the post-treatment follow-up phase (based on presence of the 'End of Treatment Phase Disposition' page and absence of the' End of Post-treatment Phase Disposition' page);

- Number (%) of patients who discontinued from the post-treatment follow-up phase (based on completion of 'End of Post-treatment Phase Disposition' page with date of discontinuation and discontinuation reasons entered under 'Subject Status');
- Number (%) of patients who entered survival follow-up from post-treatment phase (based on completion of 'End of Post-treatment Phase Disposition' page with date of discontinuation and discontinuation reasons entered under 'Subject Status' and 'Will the subject be followed for survival' is 'Yes' for patients who discontinued from the post-treatment follow-up phase);
- Number (%) of patients who discontinued from study (based on completion of 'End of Post-treatment Phase Disposition' page with date of discontinuation and discontinuation reasons entered under 'Subject Status' and 'Will the subject be followed for survival' is 'No' for patients who discontinued from the post-treatment follow-up phase);
- Primary reasons for discontinuation from the post-treatment follow-up phase (based on discontinuation reasons entered under 'Subject Status' in the 'Post-treatment Phase Completion' page).

3.2.5 Study treatment

Duration of exposure to study drug, cumulative dose, average daily dose, DI and RDI (including categories: <50%, 50%-<75%, 75%-<90%, 90%-110%, ≥110%) 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. The number of patients with dose changes, reductions and interruptions, and the corresponding reasons will be presented.

Time to first dose reduction and time to first dose interruption will be presented graphically using Kaplan-Meier methodology. Patients who did not have a dose reduction will be censored at the date of the last dose of study drug. Summary statistics of time to first dose reduction/interruption will be presented for patients with at least one dose reduction/interruption.

All information relevant to drug administration will be listed using safety set.

3.2.6 Concomitant therapy

Concomitant therapies are defined as any medications (excluding study drugs, prior antineoplastic treatments and blood transfusions), surgeries or procedures (including physical therapy) administered in the study and are recorded in the Prior and Concomitant Medications and the Surgical and Medical Procedures eCRF, respectively.

Concomitant medications will be coded using the WHO Drug Reference Listing (WHO DRL) dictionary that employs the WHO ATC classification system. Surgeries or procedures will be coded using the latest MedDRA terminology prior to database lock. All summaries will be tabulated using frequency counts and percentages.

Concomitant therapies will be summarized by ATC class and PT. Surgeries and medical procedures will be summarized by primary system organ class and PT. These summaries will include

- medications/surgeries and medical procedures starting on or after the start of study treatment but starting no later than 30 days after last dose of study treatment, and
- medications/surgeries and medical procedures starting prior to the start of study treatment but continuing after the start of study treatment.

All concomitant therapies and surgeries and medical procedures will be listed. Any concomitant therapies/surgeries and medical procedures starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing.

3.2.7 Antineoplastic therapy after discontinuation of study drug

The FAS will be used for all listings and summaries of antineoplastic therapies initiated after discontinuation of study drug. All summaries will be tabulated using frequency counts and percentages.

Antineoplastic medications initiated after discontinuation of study drug will be summarized and listed by ATC class and PT.

Antineoplastic radiotherapy and surgery information since discontinuation of study treatment will be summarized and listed.

3.2.8 Pharmacokinetic evaluation – primary analysis of the trial

The primary objective is to characterize the PK profile of LDK378 in Chinese adult patients with ALK-rearranged NSCLC previously treated with crizotinib following single and multiple once daily oral doses of LDK378.

Extensive PK assessment consisting of pre-dose trough PK, sparse post-dose PK as well as intensive PK sampling during the 5-day PK run-in period and Cycle 2 Day 1 will be collected in the first 15 enrolled patients to obtain approximately 12 evaluable full PK profiles. Separated from this subset of patients with extensive PK assessment, sparse post-dose PK samples will be collected on Cycle 1 Day 1, Cycle 1 Day 8 and Cycle 2 Day 1, in addition to pre-dose trough PK in the rest of the enrolled patients.

Only PK trough plasma concentrations with non-missing date and time and for which the last prior dose date and time are non-missing will be included in the PK analysis. Unscheduled samples are not included in summary analysis. These samples will be flagged in the corresponding concentration listing.

For patients with extensive PK data, the following PK parameters of LDK378 will be calculated from the individual concentration-time profile obtained from serial PK samples (see Table 3-1). The non-compartmental method will be used with the aid of using Phoenix WinNonlin (Version 6.2 - Pharsight, Mountain View, CA).

Among the parameters, Cmax, Tmax, AUC0-24h, AUClast and AUCinf are considered as primary; and the following are considered secondary: T1/2, T1/2, acc, Lambda_z, Racc, CL/F (or CLss/F at steady state), Vz/F.

Table 3-2 Noncompartmental pharmacokinetic parameters

Parameter	Descriptor	Primary or Secondary
AUClast	The area under the concentration-time curve from time zero to the last measurable concentration time (ng*h/mL)	Primary
AUC0-24h	The area under the plasma concentration-time curve calculated from time zero to 24 hours (ng*h/mL)	Primary
AUCinf	The area under the plasma concentration- time curve from time zero to infinity (ng*h/mL)	Primary
Cmax	The observed maximum plasma concentration following administration (ng/mL)	Primary
Tmax	The time to reach peak or maximum concentration (h)	Primary
Lambda_z	Terminal elimination rate constant (1/h)	Secondary
T1/2	Elimination half-life determined as 0.693/lambda_z (h)	Secondary
T1/2,acc	The effective half-life determined according to Racc (h)	Secondary
Racc	Accumulation ratio calculated using AUCtau, ss/AUCtau, sd where tau is the dosing interval	Secondary
CL/F	The total body clearance from plasma (L/h). CLss/F is calculated from AUCtau assuming steady state (CLss/F = Dose/AUCtau) (L/h)	Secondary
Vz/F	The apparent volume of distribution during the terminal elimination phase (L)	Secondary

Note: the above pharmacokinetic parameter nomenclature follows Novartis internal guidance [DMPK R0900136]

LDK378 concentrations

Summary statistics, including n, mean, SD, CV for mean, geometric mean, CV for geometric mean, median, minimum and maximum, will be tabulated for concentration versus time profile of LDK378 using PAS. This will be done separately for patients in PK run-in with extensive PK assessment and the rest of the patients with sparse PK sampling. The PK concentration versus time profiles of LDK378 will also be displayed graphically for full PK profile and trough collections.

PK concentration data will be listed using FAS.

LDK378 PK parameters

Primary and secondary PK parameters except Tmax will be summarized using the same reporting approach as for LDK378 concentrations. For Tmax, median, minimum and maximum will be presented.

Using FAS, the PK parameters will be presented in listings.

Trough concentration

Evaluable concentrations at the following time points will be used: pre-dose samples (in either a full profile, or as a single pre-dose collection), 24h on C1D1 (for sparse assessment), and 24h on C2D1 for patients with extensive PK data.

The trough concentration obtained throughout the study will be plotted separately for patients in PK run-in with extensive PK assessment and the rest of patients with sparse PK sampling. Only time points with n≥4 observations will be shown in the figure.

No model based analyses will be conducted.

Average steady state (SS) Ctrough

[redacted]

Steady state trough PK concentration (SS Ctrough) is defined as evaluable trough concentrations at steady state. This means both the 15 patients in PK run-in with extensive PK assessment and the rest of patients with sparse PK sampling will be considered.

[redacted]

Inter/Intra patient variation

The intra-patient and inter-patient variations will be evaluated using data from patients with more than one steady state evaluable trough PK measurements. The intra-patient and inter-patient variations will be estimated using random effects model with patient as random effect.

[redacted]

Handling of concentrations below LLOQ or missing

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

3.2.9 Safety evaluation

All safety analyses will be performed based on the Safety Set.

Grouping for the analyses

Safety summaries will include data from the following three mutually exclusive segments:

- Pre-treatment period: from day of patient's informed consent to the day before first dose of study treatment.
- 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 after last dose of study drug

The safety summary tables will include only assessments during the on-treatment period, unless otherwise specified. For select items, shift tables or change from baseline summaries generated

for laboratory, ECG, vital signs and change score generation may use data from pre-treatment period for baseline calculations.

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

3.2.9.1 Adverse events (AEs)

Summary tables for AEs will include only AEs observed during the on-treatment period. AEs will be coded using MedDRA using the latest version available prior to clinical database lock and will be graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist 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 Phase Disposition", "Post-treatment Phase Completion" or "Death" eCRF pages.

All AE summaries will be summarized (frequency counts and percentages) by SOC and/or PT, maximum severity grades (based on CTCAE grades), and relation to study drug 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.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient. AEs leading to study discontinuation and AEs requiring dose adjustment or interruption will be listed separately.

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 SOC and PT
- SAEs regardless of study drug relationship
- SAEs suspected to be study drug related
- AEs associated with discontinuation of study drug
- AEs requiring dose adjustment or study drug interruption
- AEs requiring dose adjustment
- AEs requiring study drug interruption
- AEs requiring concomitant medication or non-drug therapy
- AEs excluding SAEs
- On-treatment deaths and serious adverse events by primary SOC and PT
- Non-serious adverse events (threshold = 5%) by primary SOC and PT

Adverse events of special interest

AESIs are defined as AEs within the following categories/ groupings of PTs:

- Hepatotoxicity
- Interstitial lung disease/Pneumonitis

- QTc prolongation
- Hyperglycemia
- Bradycardia
- GI toxicity (including nausea, diarhea, vomiting)
- Pancreatitis (including lipase or amylase increases)

AESIs are also referred to as clinically notable adverse events (CNAEs) in the protocol. CNAEs are defined at the project level and may be updated based on emergent data to reflect new CNAEs of interest at the time of analysis. The CNAEs listed above will be identified based on a list of PTs. Both the final categories of AESI and the list of preferred terms should refer to the Case Retrieval Strategy at the time of database lock, which will be finalized in a separate document. These CNAEs will be summarized for each grouping, by PT, as follows:

- All CNAEs
- CTC grade 3/4 CNAEs
- CNAEs suspected to be study drug related
- Serious CNAEs
- CNAEs leading to study drug discontinuation
- CNAEs requiring dose adjustment or study drug interruption.
- CNAEs requiring dose adjustment
- CNAEs requiring study drug interruption

3.2.9.2 Laboratory data

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

Laboratory data will be classified (by Novartis Oncology Statistical programming) into CTC grades according to the NCI CTCAE v4.03. For all reports, CTC grade is always obtained on the converted measurement in SI unit. The CTC grade 0 will be assigned as below in different scenarios:

- 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.
- 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.
- 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 lab 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).

- For CTC grades of glucose (fasting or non-fasting), glucose fasting values will be used. For glucose non-fasting values, Grade 1 or 2 will be reassigned to Grade 0.

Grade 5 will not be used. 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 the hematology and biochemistry 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.

The following lab parameters will be summarized:

- Hematology: absolute lymphocytes, absolute neutrophils, hemoglobin (anemia) , white blood cell (WBC), platelet counts , absolute basophils, absolute eosinophils, absolute monocytes, red blood cells(RBC)
- Biochemistry: alkaline phosphatase (ALP), alanine aminotransferase (ALT) , aspartate aminotransferase (AST), total bilirubin, amylase, potassium , sodium, creatinine, glucose(fasting), phosphate, albumin, calcium (corrected for albumin), magnesium, creatinine clearance, direct bilirubin, blood urea nitrogen (BUN) or urea, lipase, Gamma glutamyl transferase (GGT)

  For bi-directional parameters, both hyper and hypo summaries will be presented.
- Hormones (males only): Testosterone, LH, FSH, sex hormone binding globulin (SHBG).

In addition, for hematology and biochemistry parameters, a summary table with frequency counts and percentages of patients of new and worsen abnormalities based on CTC grade will be presented.

The following laboratory parameters will be presented in listings and will not be summarized:

- Urinalysis: macroscopic panel (dipstick) (bilirubin, blood, glucose, ketones, WBC, nitrite, pH, protein, specific gravity, urobilinogen), Urinalysis Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells).
- Coagulation: INR, pro-thrombin time (PT) or Quick Test

The following listings will be produced for the laboratory data 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.

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.

3.2.9.3 ECGs

ECG data will be analysed based on central reading. 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 study drug discontinuation 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 or log-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:

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

Log-linear regression method:

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

$$QTcLogP = \frac{QT}{RR^{\hat{b}}}$$

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 one of QTcP or QTcLogP.

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, one of QTcP or QTcLogP) and RR using individual (non-averaged) baseline assessments and separately using on-treatment assessments
- For each of the ECG parameters (HR, and QT, QTc, QRS, 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
- Frequency counts and percentages of patients having notable ECG values according to the following categories:
  - 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 at risk for a specific category. For new abnormality post baseline, the denominator is the number of patients with both a baseline and a post-baseline evaluation and baseline not meeting the criterion. 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 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 patient, time point, the corresponding notable values and abnormality findings.

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 shift table analysis of notable QT parameters.

3.2.9.4 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).

Clinically notable elevated values are defined as:

- Systolic BP: ≥ 160 mmHg and an increase ≥ 20 mmHg from baseline
- Diastolic BP: ≥ 100 mmHg and an increase ≥ 15 mmHg from baseline.
- Body temperature: ≥ 39.1°C
- Weight: increase from baseline of ≥ 10%
- Pulse rate: ≥ 120 bpm with increase from baseline of ≥15 bpm

Clinically notable below normal values are defined as:

- Systolic BP: ≤ 90 mmHg and a decrease ≥ 20 mmHg from baseline
- Diastolic BP: ≤ 50 mmHg and a decrease ≥ 15 mmHg from baseline
- Body temperature: ≤ 35°C
- Weight: decrease from baseline of ≥ 10%
- Pulse rate: ≤ 50 bpm with decrease from baseline of ≥ 15 bpm

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, diastolic BP and systolic BP.

Descriptive statistics will be tabulated for baseline and change from baseline to worst post-baseline value for each vital sign measurement.

Patients with at least one 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.

WHO performance status

ECOG performance scale is provided in Table 3-2 and is used to assess physical health of patients, ranging from 0 (most active) to 5 (dead):

Table 3-3 WHO performance scale

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

Shift tables of WHO performance status at baseline to worst post-baseline WHO status by score will be presented; shift tables of ECOG performance status at baseline to best post-baseline ECOG status by score will also be provided. WHO performance status at each time point will be listed.

3.2.10 Efficacy evaluation

All efficacy analyses will be performed based on the FAS, unless otherwise specified.

3.2.10.1 Overall response rate – key secondary objective

The key secondary objective in this study is to evaluate anti-tumor activity of LDK378 in term of ORR as assessed by the investigator per RECIST 1.1. ORR is defined as the proportion of patients with a best overall confirmed complete response (CR) or partial response (PR) per RECIST 1.1.

Best overall response

The best overall response will be assessed based on reported lesion responses at different evaluation time points. Both CR and PR must be confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met. The next scheduled assessment may be used for purposes of confirmation of response. Best overall confirmed response for each patient is determined from the sequence of overall (lesion) responses according to the following rules:

- CR = at least two determinations of CR at least 4 weeks apart before progression.

- 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) > 6 weeks after start of treatment (and not qualifying for CR or PR).
- PD = progression ≤12 weeks 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 6 weeks or progression within the first 12 weeks)

Confirmed partial or complete responses reported prior to any additional anticancer therapy will be considered as responses in the calculation of the ORR irrespective of the number of missed assessments before response. Unconfirmed PR and unconfirmed CR are considered as stable disease (SD) if > 6 weeks after start of treatment, otherwise considered as unknown. Patients who are of unknown clinical response will be treated as non-responders.

Only tumor assessments performed before the start of any further anti-neoplastic therapies (i.e. any additional secondary anti-neoplastic therapy or anti-cancer surgery) will be considered in the assessment of best overall response. Further anti-neoplastic therapies will be identified via protocol deviations or from the data collected on 'Anti-neoplastic therapies since discontinuation of study drug' as appropriate. Clinical deterioration will not be considered as documented disease progression. Patients with best overall response 'unknown' will be summarized by reason for having unknown status. The following reasons will be used:

- No valid post-baseline assessment
- All post-baseline assessments have overall response UNK
- New anti-neoplastic therapy started before first post-baseline assessment
- Stable disease (SD) too early (<= 6 weeks after start date of study drug)
- PD too late (> 12 weeks after start date of study drug)

Special (and rare) cases where best overall response is 'unknown' due to both early SD and late PD will be classified as 'SD too early'.

Patients who have disease progression and continue to receive treatment after progression will qualify for progressive disease at the time of progression and will be counted as PD in ORR and other efficacy calculations.

The analysis of ORR will be performed on the FAS. The ORR will be estimated and the 95% confidence interval (CI) based on the exact binomial distribution will be provided.

Supportive Analyses

The supportive analyses will be based on BIRC assessment of ORR for FAS. The analysis of ORR will also be repeated using PPS.

Concordance/discordance of best overall response between BIRC and investigator assessments will be summarized and also presented in detail by listings. Waterfall plots representing the best percentage change from baseline in the sum of the tumor measured diameters for target lesions will be produced.

3.2.10.2 Other secondary efficacy objectives

The other secondary efficacy objectives are:

- To evaluate DOR, DCR, TTR, OIRR and PFS both by investigator assessment and BIRC assessment
- To evaluate ORR and OIRR by BIRC
- To evaluate OS

Duration of Response

Among patients with a confirmed response (PR or CR) per RECIST 1.1 by investigator, DOR is defined as the time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause. If a patient has not had an event, DOR is censored at the date of last adequate tumor assessment.

The censoring and event date options to be considered for the DOR analysis follow those for PFS below.

DOR will be described in tabular and graphical format using Kaplan-Meier methods including estimated median (in months) with 95% CI, 25th and 75th percentiles (Brookmeyer and Crowley 1982, Klein and Moeschberger 1997) and Kaplan-Meier estimated probabilities with corresponding 95% CIs (Kalbfleisch and Prentice 1980) at several time points (including at least 3, 6, 9, 12, 15 and 18 months).

Refer to Section 4.2.3.3 for further details regarding derivation of Kaplan –Meier estimates.

Disease control rate

DCR, defined as the proportion of patients with best overall response of CR, PR, SD, or Non-CR/Non-PD per RECIST 1.1 by investigator will be estimated and the 95% CI (Clopper & Pearson, 1934) based on the exact binomial distribution will be provided.

Time to response

Time to overall response of CR or PR (TTR) is defined as the time from start of study drug to first documented response (CR or PR, which must be confirmed subsequently) for patients with a confirmed CR or PR.

TTR will be summarized in 2-month intervals using descriptive statistics. The analysis will be performed based on investigator assessment.

Progression-free survival

PFS is defined as the time from the date of first dose of study drug to the date of the first documented disease progression per RECIST 1.1 by investigator, or death due to any cause.

If a patient has not progressed or is not known to have died at the date of analysis cut-off or has received any anticancer therapy other than study drug, 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. Refer to Table 3-3 for censoring and event date options and outcomes for PFS.

In particular, PFS will be censored at the last adequate tumor assessment if one of the following occurs: absence of event; the event occurred after a new anticancer therapy is given; the event occurred after two or more missing tumor assessments (see Section 4.2.1). See also Section 4.2.1 describing the special case of a missing baseline tumor assessment.

PFS will be described in tabular and graphical format 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 3, 6, 12, 18 and 24 months). Censoring reasons will also be summarized (see Section 4.2.1)

Table 3-4 Outcome and event dates for PFS and DOR analyses

Situation		Date	Outcome
A	No baseline assessment	Date of first dose of study drug [a]	Censored
B	Progression at or before next scheduled Assessment	Date of progression	Progressed
C1	Progression or death after exactly one missing assessment	Date of progression (or death)	Progressed
C2	Progression or death after two or more missing assessments	Date of last adequate assessment	Censored
D	No progression	Date of last adequate assessment	Censored
E	Treatment discontinuation due to 'Disease progression' without documented progression, i.e. clinical progression based on investigator claim	N/A	Information ignored. Outcome derived based on radiology data only.
F	New anticancer therapy given	Date of last adequate assessment	Censored

[a] The rare exception to this is if the patient dies no later than the time of the second scheduled assessment as defined in the protocol in which case this is a PFS event at the date of death

In addition, summary tables of PFS by brain metastasis at baseline status (presence vs. absence) will be generated by investigator and BIRC assessment respectively.

Overall survival

OS is defined as the time from the first dose of study drug to the date of death due to any cause. If the patient is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cutoff date (see Section 4.1.4 for further details on derivation of last contact date).

OS will be described in tabular and graphical format 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 3, 6, 12, 18 and 24 months). Censoring reasons ('Alive' or 'Lost to follow-up') will be summarized. Patients not known to have died will be censored for 'Lost to follow-up' if the time between their last contact date and the analysis cut-off date is longer than four cycles plus 2 weeks, i.e., 18 weeks for this study.

Overall intracranial response rate

OIRR is calculated based on response assessments in the brain for patients 1) having both measurable and/or non-measurable brain metastases at baseline (i.e. at least one target/and or non-target lesion in the brain); 2) having measurable brain metastases at baseline (i.e., at least one target lesion in the brain). OIRR is defined as the proportion of patients with a best overall confirmed response of CR or PR in the brain, as assessed per RECIST 1.1 by the investigator.

OIRR will be estimated and the 95% CI based on the exact binomial distribution will be provided. For details on the OIRR calculations see section 4.2.4.

The following analyses will be performed:

- Best overall intracranial response per investigator assessment (Full analysis set - Patients with measurable and/or non-measurable disease in the brain at baseline as per investigator review)
- Best overall intracranial response per investigator assessment (Full analysis set – patients with measurable disease in the brain at baseline as per investigator review)

Supportive analyses

DOR, DCR, TTR, PFS and OIRR will also be assessed by BIRC using the same analytical conventions as analysis by investigator assessment and serve as the basis of supportive analysis.

Duration of Follow-up and Gap Analyses

Follow-up in the study will be summarized using the following methods to provide a comprehensive assessment of follow-up for all patients.

Summary of duration between start date of study drug and cut-off date, and follow-up times for PFS/OS, are defined as follows:

- Duration between start date of study drug and data cut-off date = (Cut-off date – Start date of study drug + 1) / 30.4375 (months).
- Follow-up time = (Date of event or censoring – Start date of study drug + 1) / 30.4375 (months) regardless of censoring. Date of censoring is defined as the last adequate tumor assessment date for PFS or last contact date (when the patient is known as alive) for OS.

Summaries will also be tabulated for the gap time for PFS/OS follow-up compared to the cutoff date. Gap analysis is the summary of gap time (months) for PFS/OS follow-up as compared to cut-off date. Gap time for PFS/OS is defined as follows

- For patients who are censored regardless of follow-up status,

  Gap time = (data cut-off date – censoring date)/30.4375 (months).

- For patients who completed study phase or prematurely discontinued from the study due to certain reasons e.g. withdraw consent, lost to follow-up,

  Gap time = (min(data cut-off date, study discontinuation date)- censoring date)/30.4375 (months).

- For patients who are censored but still in follow-up, Gap time = (data cut-off date – censoring date)/30.4375 (months).

Quartiles, minimum and maximum as well as the frequency count and percentage of patients in each of <4, 4-<8, 8-<12, 12-<18, ≥18 months will be reported for PFS and OS gap time for patients who were censored.

All summaries will be reported in months (see Section 4.1.5). The calculations for PFS will be based on investigator assessment. Date of censoring is the same as defined for the PFS and OS analysis.

3.2.12 Interim analysis

An interim analysis will be performed after the first 30 patients enrolled have completed at least 4 cycles of treatment with LDK378 or have discontinued earlier. The interim analysis will focus on full pharmacokinetics profile, safety and preliminary efficacy data listed as below. For details on the extent of interim analysis, please refer to appendix 1 List of output for interim analysis

- Pharmacokinetics: A statistical analysis will be performed on the PK data. Plasma concentration of LDK378 and PK parameters will be summarized and listed.
- Safety: all adverse events observed by the data cutoff date will be summarized and listed. Separate summaries will be provided for SAE and death, respectively. Abnormal results on laboratory assessment and ECG will be presented and listed in detail.
- Efficacy: ORR observed by the data cutoff date will be estimated with corresponding binomial exact 95% CI.

3.3 Section 9.7.2 Sample size calculation

Overall approximately 100 patients will be enrolled This sample size was deemed to be adequate to assess safety, and tolerability and demonstrate the anti-tumor activity of LDK378 in Chinese patients.

The first 15 patients being enrolled in the phase I component will have a 5-day PK run-in period so to obtain approximately 12 evaluable PK profiles.

3.4 Power for analysis of key secondary variables

With a total of 100 patients, if the observed ORR (key secondary endpoint) is 45% (45 responders in 100 treated patients), this will results in an exact binomial 90% CI of [36.5%, 53.7%].

4 Appendix 16.1.9 of CSR- Documentation of statistical method

4.1 Statistical methods

The statistical methodologies used are described and discussed in Section 9.7 of the CSR. In Section 16.1.9, details of the statistical methods and their justification are provided for the statistical reviewers.

All analyses will be performed using SAS® Version 9.4 (or later version if available at time of database lock).

4.1.1 Difference between SAP and protocol

Not applicable.

4.1.2 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 report. For these events, the end date will not be imputed and therefore will not appear in the listings.

For patients known to have died prior to or on 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 have the end date imputed to the death date.
- This approach applies, in particular, to AEs and concomitant medication report. For these events, the imputed end date 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 treatment after the cut-off date), the end date will be imputed to the min (cut-off date, death date, 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.

4.1.2.1 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 4-1 explains the abbreviations used.

Table 4-1 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 4-2 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 4-2 AE partial date imputation algorithm

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

The following Table 4-3 is the legend to the above table.

Table 4-3 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 4-4 gives a few examples.

Table 4-4 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

4.1.2.2 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.

4.1.2.3 Incomplete date of initial diagnosis of cancer, date of first recurrence/progression 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.

If the imputed first recurrence date is after recent recurrence date, use the recent recurrence date as first recurrence.

If the imputed recent recurrence date is before the first recurrence, use the first recurrence date as the most recent recurrence.If both first recurrence and recent recurrence are imputed and the imputed first recurrence is after the recent recurrence, then use the imputed recent recurrence as the first recurrence date.

4.1.2.4 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 treatment -1'.

End date:

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

Imputed date = min (start date of study treatment, 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 treatment + 1, first day of the month), if day is missing;

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

End date: No imputation

4.1.2.5 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 1st of the month is used.

If the month is not completed, for any of the investigations, the respective assessment will be considered to be at the date which is exactly between 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.

4.1.2.6 Incomplete date for death or last contact

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

If the day or month 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: 15th day of the month and year of death
- Missing day and month: July 1st of the year of death

If the day is missing from the date of last contact it will be imputed to 15th day of the month and year of last contact only if derived from the survival page.

4.1.2.7 Incomplete dates for disease progression on Crizotinib prior to the start of study drug.

If day of progression associated with the 'Prior Antineoplastic Therapy – Crizotinib' page is missing then the imputed PD date is:

= min (midpoint between the end date of the prior crizotinib medication and the end of the month, start date of LDK), if end date of prior crizotinib medication is in the same month as the PD date.

= min (15th of the month of the PD date, start date of LDK), if end date of prior crizotinib medication is in a month prior to the PD date.

= 15th of the month of the PD date, if end date of crizotinib medication is in a month after the PD date.

If both day and month of progression associated with the 'Prior Antineoplastic Therapy – Crizotinib' page is missing then the imputed PD date is:

= min (midpoint between the end date of the prior crizotinib medication and the end of the year, start date of LDK) if end date of prior crizotinib medication is in same year as the PD date

= min (July 1 of the year of the PD date, start date of LDK), if end date of prior crizotinib medication is in a year prior to the PD date.

= July 1 of the year of the PD date, if end date of prior crizotinib medication is in a year after the PD date.

Completely missing PD dates will not be imputed. For the midpoint calculation, if odd days in between (e.g last dose of criztonib is 27 June 2012, and end of the month is 30 June 2012), then use the next day from the midpoint calculation (e.g midpoint is 29 June 2013).

4.1.2.8 Incomplete dates for last dose of study drug

Scenario 1

If the last date of study drug is after the cut-ff 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 Year = Year of min (EOT date, death date) and Month < the month of min (EOT date, death date)

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

The imputed date will be compared with start date of study drug.

If the imputed date < start date of study drug, then last date of study drug is set to start date of study drug;

Otherwise, use the imputed date.

4.1.3 Laboratory data

This section provides further detail on the laboratory parameters that will be listed and summarized as described in Section 3.2.9.2.

Hematology

Hematologic tests include: a complete blood count (CBC) consisting of RBCs, a total white blood cell count (WBC) with differential (total neutrophil [including bands], lymphocyte, monocyte, eosinophil, and basophil counts), hemoglobin, and platelet count.

The following rules will be applied to derive the WBC differential counts when only percentages are available (this is mainly important for neutrophils and lymphocytes, because the 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 the 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 % range missing and absolute range missing, then use pre-defined normal range reported in the Merck manual
- 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.

4.1.4 Last contact date

The last contact date is used for censoring in the OS analyses and will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- All patient assessment dates (blood draws (laboratory, PK), vital signs, performance status, [redacted], ECG, tumor assessments)
- Start and end dates of antineoplastic therapies administered after study treatment discontinuation.
- AE start and end dates
- Last date of contact collected on the 'Survival information' eCRF (do not use if answer to question 'Is subject alive ?' is 'Unknown')
- Study drug start and end dates
- Date of discontinuation on the 'End of Treatment Phase Disposition' and/or the "End of post-treatment phase disposition" eCRFs.

Only dates associated with patient visits or actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used. Assessment dates after the cutoff date will not be applied to derive the last contact date.

4.1.5 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.

4.1.6 Dose interruptions and dose changes

This section provides additional details to those included in Section 3.1.1.4.

All calculations of dose interruptions and dose changes are based on 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.

- For the first 15 patients who are planned to receive a single dose on the first day of the PK run-in period, the rest four days of PK run-in period will not be counted as an interruption.
- 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.

4.2 Efficacy endpoints

For further details on efficacy endpoints, see Section 14 (Appendix II) of the protocol. For the evaluation of tumor-response related endpoints, response is assessed by investigator and BIRC according to RECIST 1.1.

Response and progression evaluation will be performed according to the Novartis RECIST 1.1 guidelines, included in Section 14 (Appendix II) of the LDK378A2109 protocol.

The text below gives more detailed instructions and rules needed for programming of the analyses described in Sections 3.2.10

4.2.1 Implementation of RECIST guidelines

Disease progression

PD should only be assigned if it is confirmed by an objective assessment method as per RECIST 1.1 (e.g. radiologic scan, histology for bronchoscopy, photos for skin lesions). If a new lesion is detected using an objective assessment method other than radiologic scan, it should be entered on the 'New lesion' RECIST 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 best overall response, the derivation of any efficacy endpoint or efficacy analysis.

Change in imaging modality

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 (unknown) overall lesion response assessment. A change from conventional to spiral CT and vice versa while keeping same contrast use (e.g. switching from spiral CT with contrast to CT with contrast) is not considered a change in imaging modality. However, a response assessment other than the Novartis calculated UNK response may be

accepted from the investigator or BIRC if a definitive response assessment can be justified based on the available information. Potential discrepancies between the modality used and overall lesion response reported by the investigator (e.g. change in modality but investigator assessment of response is different from UNK) will be queried during the data validation process.

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 II) of the LDK378A2109 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. In this study, the protocol defined schedule of tumor assessment is every 8 weeks 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 $D_1 = 8+2 = 10$ weeks means one missing assessment and any distance larger than $D_2 = (2*8) + 2 = 18$ weeks means two missing 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: Initiation of new cancer therapy

6: Event after >=2 missing tumor assessments

PFS censoring reason is then derived by the following sequence of rules.

- If patient is considered to have a PFS event then PFS censoring reason is set to missing.
- Else if patient has had no baseline assessment then PFS censoring reason = 4

- Else if patient has a PFS event after two or more missing assessments (If (PFS Event date <= Censoring date and (PFS Event date - Date of LATA) >= D2)) then CNSRREAS=6:
- Else if patient has no PFS event, and patient is censored at a date after two or more missing assessments ((Censoring date - Date of LATA) >= D2) then CNSRREAS = 4
- Else if censoring date equals the start date of further anti-neoplastic therapy (NWTHYDT) then CNSRREAS = 5
- Else if Censoring date equals date of discontinuation due to consent withdrawal (IFCWDDT) then CNSRREAS = 3
- Else if Censoring date equals date of discontinuation due to loss to follow-up (LOSFUDT) then CNSRREAS = 2
- Else if the Censoring date equal the analysis cut-off date and the time between LATA and the cut-off is greater than D2 days then CNSRREAS = 4
- Else if the Censoring date equal the analysis cut-off date and the time between LATA and the cut-off is less than or equal to D2 days then CNSRREAS = 1

Where min date = minimum of non-missing (analysis cut-off date, start date of further anti-neoplastic therapy, date of withdrawal of consent, date of discontinuation due to loss to follow-up)

Non-measurable disease at baseline

As specified in Section 14 (Appendix II) of the LDK378A2109 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. These patients will be included in analyses based on FAS including patients with either measurable or non-measurable disease and will be excluded from the analyses based on PPS.

As specified in Table 14-8 of Section 14 (Appendix II) of the LDK378A2109 protocol, overall lesion response can be derived for patients without measurable disease at baseline.

Missing baseline tumor assessment

As specified in Table 14-9 of Section 14 (Appendix II) of the LDK378A2109 protocol, 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 date of treatment start. 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 treatment start date will be counted as having an event in the primary analysis of PFS. All deaths will be counted in the OS analysis regardless of presence or absence of the baseline tumor assessment.

Construction of waterfall graphs

The waterfall graphs will be used to depict the anti-tumor activity. These plots will display the best percentage change from baseline in the sum of the diameter of all target lesions for each patient. The proportions of patients with various degrees of tumor shrinkage or growth can then represent a useful efficacy metric.

However, caution needs to be paid to the assessments, where an occurrence of a new lesion or worsening in non-target lesions (resulting in PD as an overall lesion response at given assessment) contradicts the measurements obtained on target lesions. These assessments will not be displayed as bars in the graph. If such a "contradicting" assessment represents the only post-baseline assessment for a patient, then the patient will be represented by a special symbol (e.g. *) in the waterfall graph.

The assessments with unknown target response and also assessments with unknown overall response will be excluded. Patients without any valid assessments will be completely excluded from the graphs.

The total number of patients displayed in the graph needs to be shown and this number will be used as a denominator when calculating the percentages of patients with tumor shrinkage and tumor growth. A footnote will explain the reason for excluding some patients (due to absence of any valid assessment).

All possible assessment scenarios are described in Table 4-5.

Table 4-5 Inclusion/exclusion of assessments used in waterfall graph

Criteria for inclusion/exclusion			Possible source of contradictions	
Target response	Overall lesion response	Include in waterfall	Non-target response	New lesion?
CR/PR/SD	PD	Yes but as * only	PD	any
CR/PR/SD	PD	Yes but as * only	any	Yes
UNK	UNK or PD	No	any	any
CR/PR/SD	UNK	No	UNK	No
CR/PR/SD	CR/PR/SD	Yes as a bar	SD/IR	No
PD	PD	Yes as a bar	any	any

The following algorithm will be used to construct the graph:

1. Select "valid" post-baseline assessments to be included, i.e. for each patient and each assessment repeat the following four steps:
   - 1.1 Check the target lesion response and overall lesion response at each assessment. If at least one of them is UNK then exclude the whole assessment. Otherwise, go to step 1.2.
   - 1.2 Check the overall lesion response. If PD, then go to step 1.3. Otherwise, go to step 1.4
   - 1.3 Check target response. If PD, then go to step 1.4. Otherwise flag the assessment✶.
   - 1.4 Calculate the % change from baseline in target lesions.
2. For each patient, go through all valid assessments identified in step 1 and find the assessment with best % change from baseline in target lesions. The "best" means best for the patient, i.e. the largest shrinkage or if a patient only has assessments with tumor

growth take the assessment where the growth is minimal. (*Example 1*: Patient 1 has the following % changes from baseline at assessments 1, 2, 3, 4 and 5, respectively: -10%; -25%; -13%; -4% and +6%. His/her best % change is then -25%. *Example 2*: Patient 2 has the following % changes from baseline at assessments 1, 2 and 3, respectively: +5%; +18% and +35%. His/her best % change is then +5%.

3. Construct the waterfall graph displaying the best % change from baseline for each patient. Patients having only ✶ flagged assessment(s) will be displayed separately.

Both BIRC assessment and investigator assessment will be used in the construction of the waterfall plot.

The recommended way of the display from left to right is:

1. Bars under the horizontal axis representing tumor shrinkage
2. Bars above the horizontal axis representing tumor growth
3. "Zero" bars with ✶ symbol representing patients with contradiction
4. '#' below or above the vertical bars represent patients with a PFS event.

4.2.2 Sources for overall lesion response

The tumor endpoints derivation is based on the sequence of overall lesion responses at each assessment/time point. However, the overall lesion response at a given assessment/time point will be provided from different sources as illustrated in Table 4-6.

Table 4-6 Sources for overall lesion response

Source 1	Investigator (local radiology) reported overall lesion response
Source 2	BIRC (Blinded Independent review committee) reported overall lesion Response

In this study, Source 1 will be used for the key secondary endpoint (ORR) derivation and other secondary endpoint calculations per investigator (DOR, DCR, TTR, OIRR and PFS).

For secondary endpoints based on BIRC assessment (ORR and OIRR), Source 2 will be used for the endpoint derivation.

4.2.3 Kaplan-Meier estimates

To analyze time to event variables (PFS, OS, DOR and TTR), 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 [Collett, 1994] for the standard error of the Kaplan-Meier estimate.

The Kaplan-Meier curves, medians and Kaplan-Meier estimates with 95% CIs at specific time points will also be displayed.

The PROC LIFETEST statement will use the option CONFTYPE=LOGLOG. The CONFTYPE option specifies the transformation applied to the survival function to obtain the point-wise confidence intervals and the confidence intervals for the quartiles of the survival times. The LOGLOG keyword specifies the complementary log-log transformation (Collett, 1994) g(x) = log (-log(x)) which ensures that the point-wise confidence intervals are always within interval [0, 1]. Although the LOGLOG is the default option in SAS v 9.1, it should be explicitly shown.

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

4.2.4 OIRR calculations in patients with measurable brain metastases

A patient with measurable brain metastases at baseline is defined as a patient having at least 1 target lesion in brain. Inclusion of response assessments based on lesion locations in the brain for each assessment (including baseline to identify whether patients have measurable brain metastases) uses the following list of terms collected based on investigator and BIRC tumor data: brain lesions, brain (multiple, right frontal, left temporal left parietal) , brain metastases (occipital, multiple, bilateral diffuse, bilateral cerebral, cerebellum), CNS, cerebellum, cerebral cortex (frontal, occipital, parietal or temporal).The following steps will be taken to calculate the best overall intracranial response (BOIR) for patients with measurable brain metastases at baseline:

1. If only target lesions in brain and no non-target lesions in brain are identified at baseline, calculate the longest diameter from all lesions in the brain (selected from list above), and new lesions in brain (if any, based on the list) to derive responses per assessment. Non-target lesion response status is not considered since no non-target lesions were identified in the brain at baseline.
2. If both target and non-target lesions in the brain are identified at baseline, calculate the longest diameter from all lesions in the brain (selected from list above), use all non-target

lesions response status in the brain (selected from list above) and new lesions in the brain (if any, based on the list) to derive responses per assessment.

3. For each assessment, derive overall intracranial response.
4. For the whole set of derived overall intracranial responses, calculate BOIR.

For this subset of patients, calculate OIRR.

4.2.5 Confidence intervals

ORR/DCR/OIRR 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% two-sided Pearson-Clopper CI. These estimates are obtained as follows:

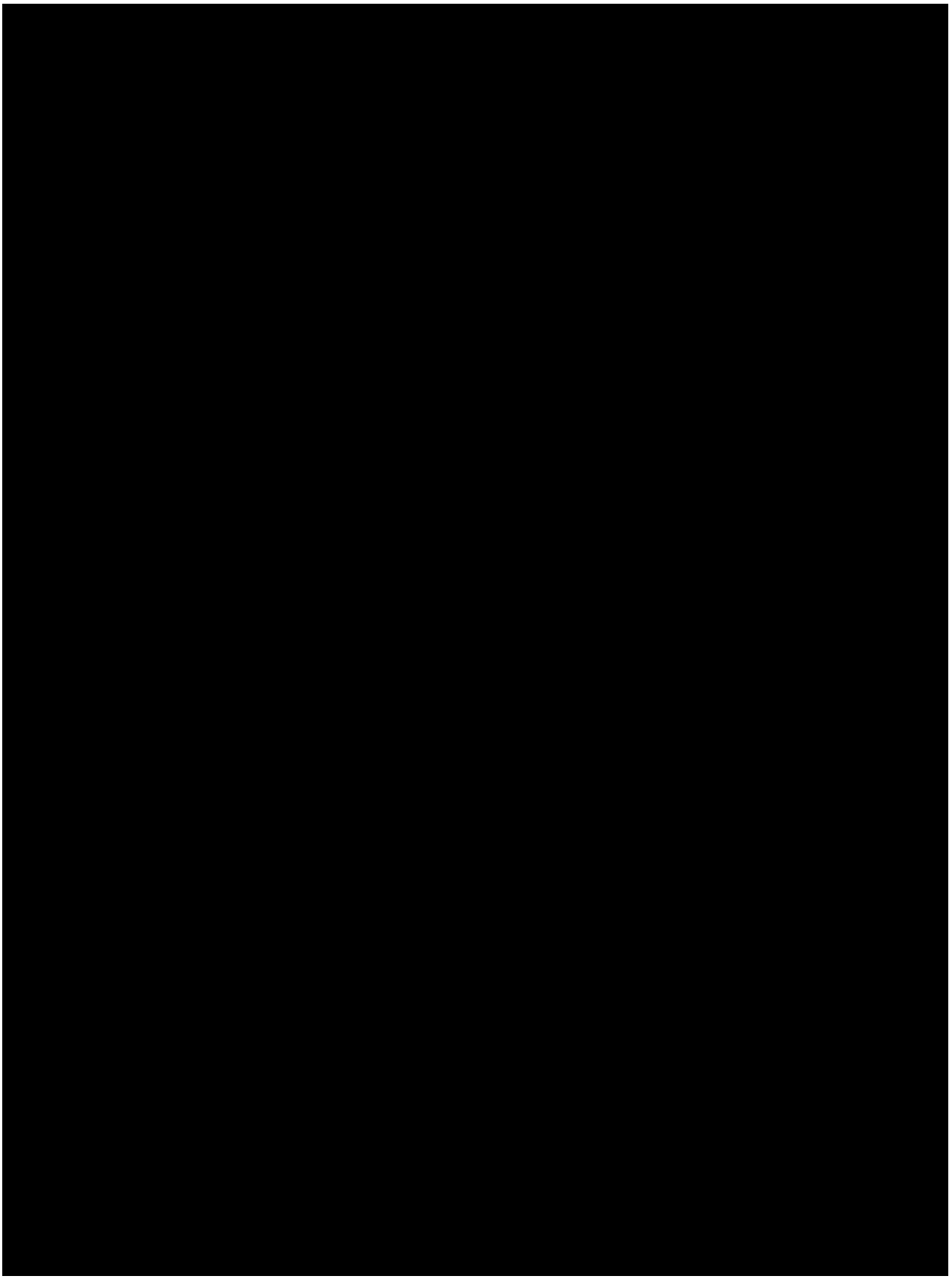
```
PROC FREQ DATA = dataset;
     TABLE binary event /
     binomial(p = null proportion level = "Yes")
     alpha = 0.05;
     EXACT binomial;
RUN;
```

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% - $LCL_{LEVEL="No"}$ (%)

[redacted]



4.4 PK analyses

The text below gives more detailed instructions and rules needed for programming of the analyses described in Section 3.2.8 .

The random effects model with subject 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 = pk dataset;
     CLASS subject;
     MODEL log_ Ctrough = / ddfm=kr solution;
     RANDOM subject;
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

[redacted]

Additional details for derivation of PK analysis set and parameters:

When deriving the PK analysis set, flags will be generated for evaluable full PK profile and evaluable sparse PK sample, as well as for each individual criterion under evaluable full PK profile and evaluable sparse PK sample (see Section 3.1.3).

When presenting figures and concentration summaries associated with full PK profile, the flag for evaluable full profile should be used; when presenting sparse PK samples related outputs, the flag for evaluable sparse sample should be used. A patient is evaluable for PK analysis if

he/she has an evaluable full PK flag or an evaluable sparse PK sample flag. In addition, evaluable trough sample flag and evaluable steady state trough sample flag will also be provided for trough samples and steady state trough sample, respectively. The evaluability criteria are the same as that for a sparse sample.

Evaluable full PK profile flag should be applied to run-in patients with extensive PK collection on the PK run-in Day 1 (from 0 hour to 120 hr post-dose sample), and C2D1 (from 0 hr to 24 hr post-dose).

Evaluable sparse PK sample flag should be applied to PK samples collected on:

- C1D8, C1D15, C3D1 to C6D1 for run-in patients
- all PK samples collected as per Table 7-7 in protocol for non run-in patients
- 0 hour pre-dose for PK run-in day 1and C2D1 for run-in patients
- 120 hr post-dose for PK run-in day 1 and 24 hr post-dose for C2D1 for run-in patients

Evaluable trough sample flag should be applied to trough samples collected on

- all 0 hour pre-dose samples
- 120 hr post-dose in run-in for run-in patients (it is also 0 hr pre-dose on C1D1 for run-in patients)
- 24 hr for C2D1 for run-in patients (it is also 0 hr pre-dose on C2D2 for run-in patients)
- 24 hr on C1D1 for non run-in patients (it is also 0 hr pre-dose on C1D2)

4.5 First Interpretable Results

4.5.1 First interpretable results for Interim analysis

There will be a database lock following the first 30 patients enrolled have completed at least 4 cycles of treatment with LDK378. First interpretable results (FIR) are the most important statistical outputs to be delivered after this database lock. For this study, FIR at interim analysis will include:

- Table of demographics and other baseline characteristics
- Table of patient disposition
- Table of analysis sets
- Table of disease history
- Table of prior antineoplastic therapy overall and on crizotinib
- Table of duration of exposure and relative dose intensity.Table of summary of PK concentrations for LDK378
- Table of summary of PK parameters for LDK378
- Figure of geometric mean and arithmetic mean (SD) trough concentration-time profiles for LDK378

- Figure of geometric mean and arithmetic mean (SD) concentration-time profiles for LDK378
- Overall summary of adverse events
- Adverse events (at least 10%), regardless of study drug relationship, by preferred term and maximum grade (Safety set)
- SAE and death information provided in text
- Table of ALT, AST, ALP and total bilirubin abnormalities
- Table of notable ECG values
- Best overall response per investigator assessment

4.5.2 First interpretable results for primary analysis

- Table of demographics and other baseline characteristics
- Table of subject disposition
- Table of analysis sets
- Table of disease history
- Table of Prior antineoplastic therapy overall and on Crizotinib
- Table of duration of exposure and relative dose intensity
- Table of summary of PK parameters for LDK378
- Figures of geometric mean and arithmetic mean (SD) trough concentration-time profiles for LDK378
- Figure of geometric mean and arithmetic mean (SD) concentration-time profiles for LDK378
- Overall summary of adverse events and clinically notable AEs
- Adverse events (at least xx%), regardless of study drug relationship, by preferred term and maximum grade
- SAE and death information provided in text
- Table of ALT, AST, ALP and total bilirubin abnormalities
- Table of notable ECG values
- Best overall response per investigator and BIRC assessment
- Best overall intracranial response and duration of response per investigator and BIRC assessment
- Progression free survival per investigator and BIRC assessment
- Summary of Summary of duration between start of treatment and cut-off date, and follow-up time for long-term outcomes

5 Reference:

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Appendix 1: List of output for interim analysis

Tables

- Patient disposition – screening phase (Full analysis set)
- Patient disposition – treatment and post treatment phase (Full analysis set)
- Protocol deviations by deviation category (Full analysis set)
- Analysis sets (Full analysis set)
- Demographics (Full analysis set)
- Disease history (Full analysis set)
- Prior antineoplastic therapy- Overall (Full analysis set)
- Prior antineoplastic therapy – Crizotinib (Full analysis set)
- Prior antineoplastic therapy – Radiotherapy (Full analysis set)
- Summary of best overall response per investigator assessment (Efficacy analysis set)
- Reasons for best overall response equal to unknown per investigator assessment(Efficacy analysis set)
- Summary of PK concentrations of LDK378 by time point in PK run-in patients (Pharmacokinetic analysis set)
- Summary of PK concentrations of LDK378 by time point in non PK run-in patients (Pharmacokinetic analysis set)
- Summary of primary PK parameters for LDK378 (Pharmacokinetic analysis set)
- Summary of secondary PK parameters for LDK378 ((Pharmacokinetic analysis set)
- Duration of exposure to study drug (Safety set)
- Dose changes and dose interruptions of study drug (Safety set)
- Summary statistics of exposure of study drug (Safety set)
- Biochemistry laboratory values: shift table based on CTC grade (Safety set)
- New or worsened biochemistry abnormalities based on CTC grade (Safety set)
- Shift tables for ALT, AST, Alkaline phosphatase and Total bilirubin (Safety set)
- Summary of ALT, AST, Alkaline, phosphatase and Total bilirubin abnormalities (Safety set)
- Change from baseline in ECG intervals by study day and time point (Safety set)
- ECG shift table based on notable values (Safety set)
- Number and percentage of patients with notable ECG changes from baseline (Safety set)
- Summary of newly occurring ECG abnormalities (Safety set)Adverse events, regardless of study drug relationship, by primary system organ class, preferred term,and maximum grade (Safety set)

- All and grade 3/4 adverse events, regardless of study drug relationship, by preferred term (Safety set)
- On-treatment deaths, by primary cause, by primary system organ class and preferred term (Full analysis set)
- Adverse events, suspected to be study drug related, by primary system organ class, preferred term and maximum grade (Safety set)
- All and grade 3/4 adverse events, suspected to be study drug related, by preferred term (Safety set)
- Serious adverse events, regardless of study drug relationship, by primary system organ class , preferred term and maximum grade (Safety set)
- Adverse events leading to study drug discontinuation, regardless of study drug relationship, by primary system organ class, preferred term and maximum grade (Safety set)
- Adverse events requiring dose adjustment or study drug interruption , regardless of study drug relationship, by primary system organ class, preferred term and maximum grade (Safety set)
- Overall summary of Adverse events (Safety set)
- Clinically notable adverse events (Safety set)

Figures:

- Geometric mean and arithmetic mean (SD) trough concentration-time profiles for LDK378 in PK run-in patients (Pharmacokinetic analysis set)
- Geometric mean and arithmetic mean (SD) trough concentration-time profiles for LDK378 in non PK run-in patients (Pharmacokinetic analysis set)
- Geometric mean and arithmetic mean (SD) concentration-time profiles for LDK378 (Pharmacokinetic analysis set)

Listings:

- Tumor assessments and responses per investigator assessment (Full analysis set)Deaths (Full analysis set)
- Serious adverse events (Safety set)
- Adverse events leading to study drug discontinuation (Safety set)
- Adverse events requiring dose adjustment (Safety set)
- Adverse events requiring dose interruption (Safety set)
- Clinically notable adverse events (Safety set)
- Patients with laboratory abnormalities of CTC Grade 3 or 4 (Safety set)
- Treatment and study completion (Full analysis set)
- Protocol deviations (Full analysis set)
- Patient demographics (Full analysis set)

- Disease history and baseline characteristics (Full analysis set)
- Prior antineoplastic therapy – Radiotherapy (Full analysis set)
- Prior antineoplastic therapy – Medications (Full analysis set)
- Dose administration records for study drug (Safety set)
- Plasma PK concentration for LDK378 (Full analysis set)
- PK parameters for LDK378 by time point(Full analysis set)
- Adverse events (Safety set)
- Hematology: primary hematology variables (Safety set)
- Hematology: WBC and differentials (Safety set)
- Biochemistry: Liver function tests and related variables (Safety set)
- Biochemistry: renal variables (Safety set)
- Patients with worst post-baseline total bilirubin > 2xULN and ALT>3xULN(Safety set)
- ECG intervals per patients (Safety set)
- ECG findings (Safety set)