NOVARTIS

Clinical Development

LDK378

Protocol 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

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List of abbreviations

AE	Adverse event
µg	Microgram
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma (serum, or blood) concentration versus time curve
AUC0-24h	Area under the plasma (serum, or blood) concentration versus time curve from time zero to 24 hours
AUCinf	Area under the plasma (serum, or blood) concentration versus time curve from time zero to infinity
AUClast	Area under the concentration-time curve from time zero to the last measurable concentration time
AUCtau	Area under the plasma (serum, or blood) concentration versus time curve from time zero to end of dosing period
BIRC	Blind Independent Review Committee
BLRM	Bayesian logistic regression model
BUN	Blood Urea Nitrogen
CI	Confidence interval
CL	Clearance
CL/F	Apparent clearance
Cmax	Maximum (peak) concentration of drug in plasma
Cmin	Minimum (trough) concentration of drug in plasma
CMV	Cytomegalovirus
CNAE	Clinically notable adverse event
CNS	Central nervous system
CR	Complete response
CrCl	Creatinine Clearance
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
D	Entered into database
DBP	Diastolic blood pressure
DCR	Disease control rate
DHEA	Dihydroepiandrosterone
DILI	Drug Induced Liver Injury
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DMPK	Drug metabolism & pharmacokinetic
DOR	Duration of response
DS&E	Safety & Epidemiology

[redacted]

EBV	Epstein-Barr Virus
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGFR	Epidermal growth factor receptor
EML4-ALK	Echinoderm microtubule associated protein like 4-anaplastic lymphoma kinase
[redacted]	[redacted]
EOS	End of study
EOT	End of treatment
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HA	Health Authorities
hCG	human chorionic gonadotropin
HED	Human equivalent dose
Hgb	Hemoglobin
HSV	Herpes Simplex Virus
IB	Investigator's brochure
IC50	Half maximal (50%) inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IGF1R	Insulin-like Growth Factor 1 Receptor
IHC	Immunohistochemistry
ILD	Interstitial lung disease
INR	International normalized ration
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous(ly)
[redacted]	[redacted]
LFT	Liver function test
LH	Luteinizing hormone
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N/A	Not applicable
NSAIDs	non-steroidal, anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
OIRR	Overall intracranial response rate
ORR	Overall response rate

[redacted]

OS	Overall survival
OTC	Over the counter
PAS	Pharmacokinetic Analysis Set
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetics
PPS	Per-protocol set
PR	Partial response
[redacted]	[redacted]
QD	quaque diem/once daily
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia formula
Racc	Accumulation ratio
RAP	Report and Analysis Plan
RBC	Red blood count
RD	Recommended Dose
R Value	ALT/ALP in x ULN
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Steering Committee
SD	Stable disease
SEC	Safety event categories
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SHBG	Sex hormone binding globulin
SI units	Standard international units
SUSARs	Suspected unexpected serious adverse reactions
T1/2	Elimination half-life associated with the terminal slope (lambda_z) of a semilogarithmic concentration-time curve (time).
TBIL	Total Bilirubin
TKIs	Tyrosine kinase inhibitors
Tmax	The time to reach maximum plasma concentration
TTR	Time to response
ULN	Upper limit of normal
VATS	Video-assisted thoracic surgery
VEGF-A	Vascular endothelial growth factor-A
Vss	Plasma volume of distribution
WBC	White blood cells
WHO	World Health Organization
WNL	Within Normal Limits

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Control drug	A study treatment used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q 21 days)
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., before starting any of the study procedures described in the protocol)
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug”
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient number	A unique identifier number (consisting of the center number and a patient-specific number) assigned to each patient who enrolls in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature patient withdrawal	Point/time when the patient exits from the study before the planned completion of all study drug administration and assessments; all study drug administration is discontinued and no further assessments are planned, unless the patient is to be followed for progression and/or survival
Randomization number	A unique treatment identification code assigned to each randomized patient, corresponding to a specific treatment arm assignment
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later
Study treatment	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any combination or control drug(s)
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.

[redacted]

Variable	A quantity subject to variation of values used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of Consent	Withdrawal of consent occurs only when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact

Protocol summary:

Protocol number	CLDK378A2109
Title	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
Brief title	A phase I/II study of LDK378 in ALK+ advanced NSCLC previously treated with crizotinib
Sponsor and Clinical Phase	Novartis, Phase I/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	While crizotinib has a high activity in patients with ALK-rearranged NSCLC, these cancers invariably progress, typically in less than one year, because of the development of resistance to crizotinib. For these patients there is no alternative ALK-targeted therapy at relapse. Therefore, the development of ALK inhibiting TKIs (tyrosine kinase inhibitors) with clinical activity against ALK-rearranged NSCLC resistant to crizotinib is crucial. The available data from the ongoing phase I study indicate that LDK378 has been well tolerated by patients with ALK-rearranged NSCLC at doses up to the MTD of 750 mg QD, and LDK378 has substantial antitumor activity in chemotherapy-treated patients with ALK-rearranged NSCLC whose disease has failed crizotinib therapy.
Primary Objective(s) and Key Secondary Objective	Primary objectives: To characterize the pharmacokinetics of LDK378 in Chinese adult patients with ALK-rearranged NSCLC 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. Key secondary objective: To demonstrate the antitumor activity of LDK378, as measured by overall response rate (ORR) to LDK378 by investigator assessment.
Secondary Objectives	To evaluate response related endpoints as assessed by investigator: 1. Duration of response (DOR) 2. Disease control rate (DCR) 3. Time to Response (TTR) 4. Overall intracranial response rate (OIRR) 5. Progression-free survival (PFS) 6. Overall survival (OS) ORR and OIRR will also be evaluated as assessed by Blind Independent Review Committee (BIRC)

[redacted]

Study design	This is a phase I/II, open-label, multi-center study in which the pharmacokinetics, safety, tolerability and efficacy of LDK378 will be assessed in adult Chinese patients with locally advanced or metastatic NSCLC harboring a confirmed ALK rearrangement. The study includes a phase I component for the first 15 patients (5 day PK run-in period) and a phase II component for all the patients with continuous dosing. 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. Approximately 100 patients will be enrolled. For the first 15 patients enrolled in this study, patients will have an additional 5-day PK run-in period before treatment period. The pharmacokinetics profile of LDK378 in Chinese adult patients with ALK-rearranged NSCLC will be evaluated. Additional patients may be enrolled in the study with PK run-in period in case PK profiles from some of the enrolled patients are deemed not evaluable due to early discontinuation from the study or due to vomiting events on the day of PK sampling. Treatment with LDK378 750 mg qd will continue until the patient experiences unacceptable toxicity that precludes further treatment, discontinues treatment at the discretion of the investigator or patient, starts a new anti-cancer therapy and/or dies. LDK378 may be continued beyond RECIST-defined PD if, in the judgment of the investigator, there is evidence of clinical benefit. Patients who discontinue the study medication in the absence of progression will continue to be followed for tumor assessment until the time of PD.
Population	Chinese adult patients with ALK-rearranged locally advanced or metastatic NSCLC that has progressed during or after crizotinib therapy no matter whether or not previously treated with cytotoxic chemotherapy.
Inclusion criteria	Patients eligible for inclusion in this study have to meet **all** of the following criteria: 1. Histologically or cytologically confirmed diagnosis of NSCLC that carries an ALK rearrangement defined as positive using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria) or positive as assessed by the CFDA approved immunohistochemistry (IHC) test (Ventana Medical Systems, Inc) using rabbit monoclonal primary antibody assay (D5F3) and associated scoring algorithm. If documentation of ALK rearrangement is not available as described above, a test to confirm ALK rearrangement must be performed using an archival tumor obtained at or since the time of diagnosis or a new tumor biopsy obtained prior to the first LDK378 dose. The test will be performed at a Novartis designated central laboratory (by IHC test using rabbit monoclonal primary antibody assay (D5F3), Ventana Medical Systems, Inc). Patients must wait for the result of the ALK rearrangement status before initiating treatment with LDK378. 2. Age 18 years or older at the time of informed consent. 3. Patients must have stage IIIB or IV NSCLC at the time of study entry and have had progressive disease during or after crizotinib treatment whether or not previously treated with cytotoxic chemotherapy. If treated with chemotherapy, maximum 2 lines are allowed. ● Patients must have progressive disease at study entry. Patients are not eligible if crizotinib was discontinued due to toxicity. ● Patients must have received their last dose of crizotinib ≥ 1 week prior to the first dose of LDK378 and recovered from crizotinib toxicities (as defined in inclusion criteria #4) ● Prior targeted therapies will not count as a line of cytotoxic chemotherapy (i.e. patients may have received prior treatment with these drugs excluding ALK-inhibitors maximum 2 lines are allowed). ● (Neo-) adjuvant cytotoxic chemotherapy will count as one prior line of treatment if relapse occurred within 12 months from the end of the adjuvant cytotoxic chemotherapy ● Note: A cytotoxic chemotherapy line in locally advanced disease is defined as an anticancer regimen that contains at least 1 cytotoxic

[redacted]

	chemotherapy agent and is given for at least 21 days or more. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression and lasted less than 21 days, then this regimen does not count as a prior line of chemotherapy 4. Patients must have recovered from all toxicities related to prior anticancer therapies to ≤ 2 (CTCAE v 4.03). The exception to this criterion is for patients with grade 2 nausea/vomiting and/or grade 2 diarrhea despite optimal supportive therapy who will not be allowed to participate in the study. Patients with any grade of alopecia are allowed to enter the study. 5. Patients must meet the following laboratory values at the screening visit: ● WBC count ≥ 4.0 x 10^9 /L ● Absolute Neutrophil Count ≥ 1.5 x 10^9/L ● Platelets ≥ 100 x 10^9/L ● Hemoglobin (Hgb) ≥ 9 g/dL ● Serum creatinine < 1.5 mg/dL and /or calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 30 mL/min ● Total bilirubin < 1.5 x ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin < 3.0 x ULN or direct bilirubin < 1.5 x ULN ● Aspartate transaminase (AST) < 2.5 x ULN, except for patients with liver metastasis, who are only included if AST < 5 x ULN ● Alanine transaminase (ALT) < 2.5 x ULN, except for patients with liver metastasis, who are only included if ALT < 5 x ULN ● Alkaline phosphatase (ALP) < 5.0 x ULN 6. Patient must have the following laboratory values WNL (within normal limits) or corrected to within normal limits with supplements during screening: ● Potassium ● Magnesium ● Phosphorus ● Total calcium (corrected for serum albumin) 7. Life expectancy ≥ 12 weeks. 8. World Health Organization (WHO) performance status 0-2. 9. At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation. 10. Written informed consent for the main study must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness. 11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.
Exclusion criteria	Patients eligible for this study must not meet **any** of the following criteria: 1. Patients with known hypersensitivity to any of the excipients of LDK378 (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate). 2. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms. 3. History of carcinomatous meningitis. 4. Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type. 5. Patient has clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months), such as: ● Unstable angina within 6 months prior to screening ● Myocardial infarction within 6 months prior to screening

[redacted]

	● History of documented congestive heart failure (New York Heart Association functional classification III-IV) ● Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening ● Ventricular arrhythmias ● Supraventricular and nodal arrhythmias not controlled with medication ● Other cardiac arrhythmia not controlled with medication ● Corrected QT (QTc) > 470 msec using Fredericia correction (QTcF) (QTcF = QT/RR1/3) on the screening ECG 6. Prior therapy with other investigational ALK inhibitors (only prior treatment with crizotinib is allowed). 7. Patients who have received thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment is allowed. 8. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting study drug or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study ≥1 week after the procedure. 9. Patients receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with LDK378 and for the duration of the study (see Appendix 1): ● Strong inhibitors or strong inducers of CYP3A4/5 ● Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5, and/or CYP2C9 ● Medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes 10. Impairment of GI function or GI disease that may significantly alter the absorption of LDK378 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome). 11. Patients who are currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants. 12. Patients receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms, (other than CNS-related), dose must have been stabilized (or decreasing) for at least 5 days before first dose of study treatment. 13. Patients receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patients on non enzyme-inducing anticonvulsants are eligible. 14. Investigational agents within 4 weeks or ≤ 10 × half-life of the agent (whichever is longer) before first dose of study treatment. 15. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. 16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during the study and for 3 months after stopping LDK378 treatment. Highly effective contraception is defined as any of: ● Total abstinence: when this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of

[redacted]

	contraception]. ● Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment. ● Male partner sterilization (at least 6 months prior to screening). (With the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female patients on the study the vasectomized male partner should be the sole partner for that patient]. ● Use of a combination of any two of the following (a+b or a+c or b+c): a. Use of oral, injected or implanted hormonal methods of contraception that have comparable efficacy (failure rate < 1%), for example hormonal vaginal ring or transdermal hormone contraception. b. Placement of an intrauterine device (IUD) or intrauterine system (IUS) c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository. In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment. Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential. 17. Sexually active males must use a condom during intercourse while taking the drug and for 3 months after stopping LDK378 treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid. 18. Other severe, acute, or chronic medical including uncontrolled diabetes mellitus or psychiatric conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results. 19 History of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
Investigational and reference therapy	LDK378 (750 mg daily)
Efficacy assessments	Radiological Tumor Assessment Response will be determined locally according to the Novartis guideline (Appendix 2) on the Response Evaluation Criteria in Solid Tumors (RECIST), based on RECIST Version 1.1 (Eisenhauer et al 2009) as evaluated by investigator assessment. Additionally, imaging data will be centrally collected, checked for quality and independently reviewed by an imaging vendor designated by Novartis and will be the basis of supportive analyses. CT/MRI scans will be performed at baseline within 28 days before start of treatment and subsequently every 8 weeks from treatment start until progression of disease. See Table 7-1 for details. Tumor imaging procedures include: ● Chest CT/MRI ● Abdominal/Pelvic CT/MRI ● Additional radiological assessments (e.g. brain imaging, bone scan, PET) as clinically indicated
Safety assessments	Adverse Events (AEs) including:

[redacted]

	● Serious AEs (SAEs)
	● Laboratory profiles
	  ● hematology
	  ● biochemistry
	  ● urinalysis
	  ● coagulation
	  ● pregnancy test (females)
	  ● hormones (males only)
	● Physical examination
	● Vital signs
	● Electrocardiograms (ECG)
	● WHO performance status

Other assessments	Sparse and extensive PK Extensive ECG [redacted]
Data analysis	Using the PAS, PK concentration versus time profiles of LDK378 will be summarized separately for patients with extensive PK assessment and patients with sparse PK sampling. The mean and individual concentration versus time profiles of LDK378 will be displayed graphically for full PK profile and trough collections. LDK378 PK parameters, including but not limited to AUClast, AUC0-24h, AUCinf, Cmax, Tmax, Lambda z, terminal T1/2, T1/2,acc, Racc, CL/F (or CLss/F at steady state)and Vz/F, as appropriate will be derived from PK run-in patients with extensive PK assessment. All PK parameters will be summarized. The PK parameters and concentration data will be listed Safety data including adverse events, vital signs, ECG and laboratory abnormalities will be summarized and listed. For efficacy, ORR as assessed by investigator will be estimated and the binomial exact 95% CI provided. DOR will be listed by patient and described using Kaplan-Meier methods and relevant statistics. DCR will be estimated and the binomial exact 95% CI provided. PFS, and OS will be described using Kaplan-Meier methods and appropriate summary statistics. Efficacy data will be listed. [redacted]
Key words	ALK, NSCLC, LDK378

[redacted]

Amendment 3

Amendment rationale

As of 29-Sep-2015, of 103 patients treated, 66 patients have been discontinued from treatment and 37 are still receiving study treatment.

The amendment provides follow up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases in order to optimize patient safety.

Other change was implemented in this amendment: Dose guidance modification for QTc text is being updated to provide clarification on monitoring procedure.

Changes to the protocol

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

The following sections to the protocol were changed:

- List of abbreviations updated with commonly used abbreviations
- Table 6-3: "Refer to Section 6.2.4.2 for additional follow-up" was added for AST or ALT and concurrent Total bilirubin management. Follow-up description updated for Grade 3 QTc interval prolonged.
- Section 6.2.4.2: Updated on following up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases to align with Novartis Oncology trial standard language.

IRB/IEC

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

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

[redacted]

Summary of previous amendments

Amendment rationale

As of the release date of this amendment the recruitment has been completed. 125 patients have been screened in the study, and 103 have been treated.

This amendment has been implemented to include availability of new safety data and to clarify sections of the protocol where additional guidance was required:

- Updates to the protocol have been made based on currently available safety data. Pancreatic enzyme elevations (lipase and/or amylase) occur in patients treated with LDK378. Clinical data suggest that a small proportion (<1%) of patients treated with LDK378 can develop clinical pancreatitis, and the causal role of LDK378 in these cases cannot be excluded. Due to this finding, the protocol has been amended to include additional dose modification and follow up monitoring language for patients who may experience this safety finding.
- The definition of end of the study has been clarified.
- The guidance regarding study treatment discontinuation and withdrawal of consent has been clarified.
- Editorial changes and text corrections were made for clarification where required.

Changes to the protocol

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

The following sections to the protocol were changed:

- List of abbreviations updated with commonly used abbreviations
- Glossary of terms updated with definitions for biological samples, study drug discontinuation and withdrawal of consent
- 'Changes to the protocol' section of the amendment 1 rational updated
- Section 1.2.1.1.3: Updated nonclinical PK and metabolism data from recent studies.
- Section 1.2.1.2.1 and Section 1.2.1.2.2: clinical safety and tolerability and clinical efficacy data updated
- Section 1.2.1.2.4: added new sentence about impact of fat content on LDK378 absorption
- Section 1.3: New section 'Risk and Benefits' added
- Table 1-3, Table 1-4 and Table 1-5 have been removed
- Section 4.1, Section 7.1.5, Section 7.1.7.2, and Section 7.2.1.2,: "Start of a new anti-cancer therapy" was removed from the list of allowable reasons to stop collection of tumor assessments.
- Section 4.3: the definition of the end of the study has been updated
- Section 6.2.1: sub-title has been updated to specify that guidelines are related to toxicities other than those listed in Table 6-3

[redacted]

- Section 6.2.4.8: added new section 'Guidelines for the follow-up of laboratory pancreatic abnormalities'
- Table 6-3: updated with criteria for dose modification and dose delay of LDK378 treatment for renal, pancreatic and cardiac toxicity
- Table 6-4: updated instructions on follow-up evaluations in case of pancreatic toxicity
- Section 6.3.1.2: updated bisphosphonates use and interaction with LDK378
- Section 6.3.1.5: updated with LDK378 dosing guidance in association to radiotherapy and surgical resection in order to align with program level language
- Section 6.3.1.6: updated to align with program level language
- Section 6.3.2.6: clarification that concomitant use of medications that are CYP2C9 and CYP3A4/5 substrates with narrow therapeutic index is not permitted with LDK378
- Table 7.1: Protocol sections numbers have been updated
- Section 7.1.5: section renamed 'discontinuation of study treatment'. Content of Sections 7.1.5.1 and 7.1.5.1.1 added to Section 7.1.5. Sections 7.1.5.1 is now 'replacement policy'. Discontinuation of study treatment and withdrawal have been clarified.
- Section 7.1.6: added new section 'withdrawal of consent'. Consequently section 'Follow up period' and related subsections were renumbered.
- Section 7.1.7.4: definition of lost to follow up has been clarified
- Table 7-3: Lipase has been added to blood chemistry
- Section 8.1.3: adverse events of special interest have been clarified
- Section 3 Table 3-1, Section 10.4.1.1 and Table 10-1: PK parameters have been clarified
- Section 10.5.3: added clarification for "on-treatment period".
- Section 10.8: details of the interim analysis have been clarified
- Editorial and typographical changes throughout the document as required

IRB/IEC

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

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

Amendment 1

Amendment rationale

As of the release date of this amendment, 61 patients have been screened to the study, and 50 have been treated. [redacted] to clarify sections of the protocol where additional guidance was required.

Main changes include:

[redacted]

- [redacted]
- [redacted]

Other changes include:

- Clarification of Exclusion Criterion 16 to include Male partner sterilization (at least 6 months prior to screening).
- Clarification of Inclusion Criterion 3 to include washout period for previous crizotinib treatment.
- Update on safety data from ongoing study [redacted] to the background section.
- Update from safety data to the dose modification guidance with LDK378.
- Update from safety data to the criteria for interruption and re-initiation of LDK378 treatment table.
- Clarification that additional patients may be enrolled in the PK run-in period.
- Addition of treatment guidance for concomitant medication treatment with bisphosphonates.
- Updated treatment guidance for gastric protection agents.
- Clarification on the statistical analysis sections.
- In addition, editorial changes and text corrections were made for clarification, where required.

Changes to the protocol

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

The following sections to the protocol were changed:

- Section 1.2.1: inclusion of FDA approval of LDK378 (ceritinib) under trade name Zykadia™.
- Section 1.2.1.1.3: updated nonclinical PK and metabolism data from recent studies. Evaluation of DDI potential was re-conducted. Using both FDA and EMA 2012 DDI guidance, the mechanistic static model determined that the inhibitory potential of LDK378 is low for CYP2C8 and CYP2B6 (AUCR <1.25). Sentence regarding LDK378 being a potent reversible inhibitor of CYP2C8 and CYP2B6 was therefore removed.
- Section 1.2.1.1.4: updated to include LDK378 and reference of IB.
- Section 1.2.1.2.1: clinical safety and tolerability updated from ongoing study CLDK378X2101.
- Section 1.2.1.2.2: clinical efficacy updated from ongoing study [redacted]
- Section 1.2.1.2.4: clinical PK data updated from recent clinical PK studies.

[redacted]

- Section 2.1: data added from ongoing study [redacted] regarding responses of LDk378 in ALK positive NSCLC.
- Section 2.3: rationale for LDK378 dose and regimen selection further clarified.
- Section 4.1: updates made to study design that additional patients may be enrolled in the study with PK run-in period in case PK profiles from some of the enrolled patients are deemed not evaluable due to early discontinuation from the study or due to vomiting events on the day of PK sampling.
- Section 4.2: the timing of interim analysis has been updated to be after 30 patients completed 16 weeks (4 cycles).
- Section 4.3 updated terminology for the rollover study.
- Section 5.2: updated inclusion criterion 3 to include washout period for previous crizotinib treatment.
- Section 5.3: updated prohibited medications.
- Section 5.3: exclusion criterion 16 to include Male partner sterilization (at least 6 months prior to screening).
- Table 6-3: updates to criteria for the interruption and re-initiation of LDK378 treatment based on updated safety data.
- Section 6.3.1.1: clarifications on corticosteroid use.
- Section 6.3.1.2: addition of bisphosphonate treatment guidance.
- Section 6.3.1.3: clarification for drugs that are metabolized by CYP450 enzymes.
- Section 6.3.2.3: updates to section regarding warfarin and coumarin derivatives.
- Section 6.3.2.6: removal of CYP2C8 substrate.
- Section 6.3.2.7: updates on gastric protection agents.
- Section 6.3.2.9: updated information on QTc prolongation from updated clinical data.
- Section 7.1.2: clarification under the screening section was added: The cardiac eligibility criteria should be assessed with the central ECG report.
- Section 7.1.3, 7.2.3 and 10.4.2.1: updates to section regarding the enrollment of Additional patients may be enrolled in the study with PK run-in period in case PK profiles from some of the enrolled patients are deemed not evaluable due to early discontinuation from the study or due to vomiting events on the day of PK sampling.
- Section 7.2.3: update volume sampling for PK tubes from 1.5 mL to 2 mL to reflect actual tube size used by central laboratory. Removal of redundant language regarding laboratory manual.
- Section 9.3: deletion of non-applicable language on IRT data transfers.
- Section 10.1.1: deletion of non-applicable language for screening failures.
- Section 10.1.5: updates to clarify pharmacokinetic analysis set (PAS) language.
- Section 10.4.1: minor update to list of LDK378 PK parameters that will be derived for PK run-in patients.
- Section 10.4.2.1: Update to non-compartmental method program language. Minor revisions to summary statistics wording.

[redacted]

- Section 10.5.2.1: minor changes to endpoint analysis for other secondary objectives.
- Section 10.5.3.2: minor changes to adverse event section to bring clarity and to align with LDK378 program.
- Section10.8: The timing of primary analysis has been updated to be after all 100 patients completed 24 weeks (6 cycles).
- Section 10.9: [redacted]
- Section 10.10: [redacted]
- Appendix 14.1: Table title for prohibited concomitant medications requiring caution updated with a notation for LDK378, deletion of CYP2C8 substrates and paclitaxel and updated footnotes for clarification.
- Appendix Table 14-2: list of medication to be used with caution updated and deletion of CYP2B6 and CYP2C8 substrates, addition of simvastatin, removal of clarithromycin and telithromycin.
- Editorial and typographical changes through the document as required.

IRB/IEC

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

[redacted]

1 Background

1.1 Overview of disease pathogenesis, epidemiology and current treatment

1.1.1 Locally advanced or metastatic non-small cell lung cancer (NSCLC)

Lung cancer has been the most common cancer in the world for several decades. In 2008, there were an estimated 1.61 million new cases, representing 12.7% of all new cancers worldwide. It was also the most common cause of death from cancer, with 1.38 million deaths (Ferlay et al 2010). In 2012, an estimated 160,000 deaths were expected in the US (Siegel et al 2012) and 262,000 in the European Union (Malvezzi et al 2012). In China in 2005, there were 497,908 new cases and 428,936 deaths, the highest one among for all malignant tumors (Wu et al 2007). Particularly in males, the highest lung cancer incidence rates are in Central and Eastern Europe (57.0 per 100,000 by age-standardized), Southern Europe (49.0), North America (48.5) and Eastern Asia (45.0). Chinese women have higher lung cancer rates (21.3 cases per 100,000 females) than those in European countries such as Germany (16.4) and Italy (11.4) (Jemal et al 2011).

The World Health Organization (WHO) divides lung cancer into 2 major classes: non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC accounts for more than 85% of all lung cancer cases including 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types); and (2) squamous cell (epidermoid) carcinoma. Adenocarcinoma (40% of lung cancers) is the most common type of lung cancer seen in the United States and is also the most frequent cell type in nonsmokers (NCCN Guidelines v2. 2014).

Cigarette smoking remains the most important risk factor for lung cancer, although approximately 15% of all lung cancers are diagnosed in patients who never smoked.

The high mortality rate of lung cancer could be explained in an advanced stage for most cases; only 25-30% of new NSCLC cases are diagnosed with localized disease that is potentially curable with surgery (Nguyen et al 2012). The majority of patients are diagnosed with locally advanced or metastatic disease, for which surgery is not indicated.

As summarized in the current National Comprehensive Cancer Network (NCCN) Guidelines for NSCLC, platinum-based combination chemotherapy is superior to best supportive care for patients with advanced, incurable disease (NCCN Guidelines v3. 2012). Platinum-doublet chemotherapy (cisplatin or carboplatin in combination with other chemotherapy agents, with or without bevacizumab) is standard firstline treatment of locally advanced or metastatic NSCLC, unless a patient has a known “druggable” gene mutation or aberration, and is therefore a candidate for a targeted therapy (as discussed below). Although chemotherapy has led to clinical improvements in patients with locally advanced or metastatic NSCLC, the outcome of treatment in the first-line setting remains poor, with median progression-free survival (PFS) and overall survival (OS) of 5-7 months and 10-16 months, respectively (Scagliotti 2008; Ciuleanu 2009; Ettinger 2010; Paz-Ares 2012).

[redacted]

Overall, current treatments are not considered satisfactory for most NSCLC patients and the prognosis continues to be poor despite chemotherapy treatment, with a 5-year OS rate of only 15% (Nguyen et al 2012). In particular, the prognosis for patients presenting with advanced, incurable disease is dismal, with a 5-year OS rate of 3.7% (Howlader et al 2009).

1.1.2 Targeted therapies in NSCLC

During the last few years, improvement in the knowledge of NSCLC biology has led to the identification of molecular events crucial for malignant transformation and cancer cell survival. These aberrant molecular events serve as critical oncogenic drivers for these cancers and, therefore, represent potential therapeutic targets (Gettinger et al 2011). As a result, new targeted treatment options for these patients are evolving. Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A), and erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), have been approved for the treatment of NSCLC (Gettinger et al 2011).

The case of EGFR TKIs illustrates a new paradigm in the treatment of NSCLC. There is increasing evidence that activating mutations of EGFR define a small subset of patients with NSCLC who have sensitivity to EGFR TKIs (Ettinger et al 2010). Six randomized trials have demonstrated that patients harboring activating EGFR mutations benefit more from EGFR TKIs than from standard chemotherapy in terms or response rate, PFS, toxicity profile and quality of life. In particular, the success of EGFR TKIs highlights the importance of identifying specific NSCLC molecular drivers to appropriately direct targeted agents to specific patient populations.

1.1.3 ALK-rearranged (ALK-positive, ALK+) NSCLC

Another clinically relevant molecular subset of NSCLC is driven by recently discovered echinoderm microtubule-associated protein-like 4 (EML4) anaplastic lymphoma kinase (ALK) translocation.

ALK is a receptor tyrosine kinase of the insulin receptor superfamily that plays a role in neural development and function. It is translocated, mutated, or amplified in several tumor types, including NSCLC, neuroblastoma, and anaplastic large cell lymphoma (ALCL), and these alterations play a key role in the pathogenesis of these tumors. Other fusion partners of ALK have been described (e.g. KIF5B, TFG, KLC1 and PTPN3 (Kruczynski et al 2012), but these are less common than EML4. Preclinical experiments have shown that the various ALK fusion partners mediate ligand-independent dimerization of ALK resulting in constitutive kinase activity and in potent oncogenic activity both *in vitro* and *in vivo*. This activity can be effectively blocked by small-molecule inhibitors that target ALK.

EML4-ALK rearrangement in patients with NSCLC is a relatively rare event and is present in approximately 2-8% of NSCLCs (Scagliotti G et al 2012; Takeuchi K et al 2009; Soda et al 2007). In a small scale research in China, the proportion of EML4-ALK is 6.3% in 239 NSCLC patients (She-Juan An 2012). In another small cohort study which included 103 Chinese NSCLC patients, EML4-ALK fusion gene was identified in 11.6% (12/103) of the patients. In patients with adenocarcinoma lacking EGFR and KRAS mutations, the prevalence of EML4-ALK translocation could be as high as 42.8% (Xuchao Zhang 2010).It is most commonly seen in younger patients with adenocarcinoma histology with never or light

[redacted]

smoking history. ALK rearrangements and other oncogenic drivers such as mutant EGFR and oncogenic RAS are generally mutually exclusive, consistent with the notion that ALK rearrangement defines a unique molecular subset of NSCLC (Gainor et al 2013). In these patients, ALK rearrangements serve as a key and strong oncogenic driver for NSCLC and represent a critical therapeutic target susceptible to targeted ALK kinase inhibition.

Crizotinib, a dual c-MET and ALK inhibitor, is the first clinically available TKI targeting ALK. Crizotinib was associated with clinically meaningful response rates of 50% and 61% in two single-arm trials in 255 patients with locally advanced or metastatic ALK-positive NSCLC (Kwak et al 2010). Responses were rapid, with the majority of patients achieving an objective response within the first 8 weeks of treatment, and durable, with a median duration of response (DOR) of 48.1 and 41.9 weeks, respectively. Based on these data, crizotinib received accelerated approval under the trade name Xalkori® in the US and conditional marketing authorization in the EU under the same trade name (Ou 2011). Subsequently, crizotinib received approval in Switzerland, Japan, China, Canada, as well as other countries worldwide. The clinical benefit of crizotinib compared to chemotherapy in terms of median PFS (7.7 and 3.0 months, respectively), quality of life, and control of symptoms has been confirmed in a phase III study in the second-line setting (Shaw et al 2013), and based on these data the Food and Drug Administration (FDA) granted regular approval for crizotinib in November 2013. The most frequent adverse events (AEs) with crizotinib treatment are visual disorders, occurring in approximately 62% of patients (Ou et al 2011). Other common toxicities include gastro-intestinal (GI) disorders (nausea 53%, vomiting 40%, diarrhea 43%), edema (28%), fatigue (20%), dizziness (16%), neuropathy (13%), elevations of liver enzymes (13%) and skin rash (10%). Three AEs warranted warning and precautions in the package insert (pneumonitis, hepatic laboratory abnormalities and QT prolongation). In addition, rapid onset of hypogonadism in the majority of male patients taking crizotinib has been reported (Weickhardt et al 2012).

While crizotinib has impressive activity in patients with ALK-rearranged NSCLC, these cancers invariably progress, typically in less than 1 year, because of the development of resistance to crizotinib. For these patients there is no alternative ALK-targeted therapy at relapse. Therefore, the development of ALK TKIs with clinical activity against ALK-positive NSCLC resistant to crizotinib is crucial.

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

1.2.1 Overview of LDK378

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

In addition, LDK378 shows potent antitumor activity in crizotinib-resistant animal models (as described below), and the efficacy seen in the ongoing Phase I clinical trial in patients (with and without previous crizotinib therapy) led to the accelerated approval of LDK378 (ceritinib)

by the US FDA under the trade name ZYKADIA™ on 29-Apr-2014 for the following indication:

- 'ZYKADIA is indicated for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib'. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.'

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

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

1.2.1.1 Submissions to other health authorities worldwide have been completed in some countries and are underway in others. Non-clinical experience

1.2.1.1.1 Pharmacology

LDK378 inhibits ALK and ALK-mediated signaling pathways in a dose-dependent manner. It inhibits autophosphorylation of ALK, ALK-mediated phosphorylation of downstream signaling proteins, and proliferation of ALK-dependent cancer cells both in vitro and in vivo.

[redacted] In a kinase panel of 35 additional enzymes, LDK378 demonstrated a high degree of selectivity for ALK inhibition by inhibiting only 2 other kinases (INSR and IGF1R) but with approximately 50-fold less potency than ALK inhibition.

Preclinical data showed inhibition of the kinase activity of the NPM-ALK fusion oncogene (in Karpas299 human ALCL cells) and of the EML4-ALK fusion oncogene (in H2228 human NSCLC cells) with LDK378, which led to inhibition of cancer cell proliferation in vitro. The inhibition of the downstream signaling pathway by LDK378 correlated with the inhibition of proliferation. In addition, inhibition of NPM-ALK and EML4-ALK in mouse and rat cell xenograft models resulted in inhibition of tumor growth and tumor regression in vivo.

LDK378 was also active in cell lines with ALK amplification or expression of activating point mutations. A single dose pharmacodynamic study and multiple daily dose efficacy study performed in Karpas299 and H2228 tumor models indicated that a 70% to 80% reduction in the ALK signaling pathway is required to achieve complete tumor regression.

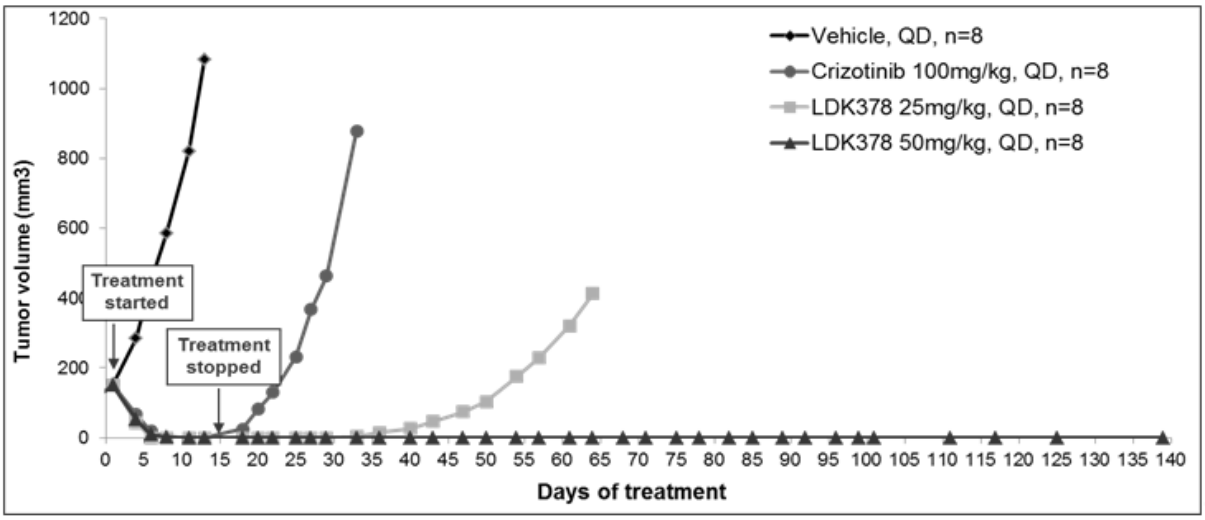
1.2.1.1.2 Antitumor activity in xenograft models

LDK378 is highly active in mouse and rat xenograft models of lung cancer and ALCL that carry an ALK rearrangement. In murine xenograft models of H2228 NSCLC and Karpas299 ALCL cells, LDK378 dosed at 25 mg/kg daily, a dose below the maximum tolerated dose (MTD) in clinical studies, resulted in complete regression of established tumors. When dosed

[redacted]

at 50 mg/kg daily for 14 days in the H2228 NSCLC model, LDK378 resulted in complete and prolonged (lasting for more than 4.5 months, the observation period) tumor regressions. In the same experiments crizotinib dosed at 100 mg/kg daily for 14 days resulted in complete tumor regression, but tumors re-grew within 2 weeks after stopping treatment (Figure 1-1).

Figure 1-1 Comparison of LDK378 with crizotinib for their anti-tumor activity in a mouse H2228 NSCLC model when dosed once a day



LDK378 also demonstrated strong antitumor activity in mouse H2228 NSCLC models that developed resistance to crizotinib after continuous treatment with crizotinib at 100 mg/kg/day. One of these crizotinib-resistant H2228 models was found to carry a secondary C1156Y mutation in the ALK kinase domain, the same mutation found in patients who progressed on crizotinib (Choi et al 2010; Huang et al 2013). While this model was resistant to crizotinib 100 mg/kg, a dose of 50 mg/kg LDK378 slowed tumor growth at the plasma exposure (AUC_{0-24h}) of 29,745 h.ng/mL. LDK378 caused complete tumor regression at 100 mg/kg after 14 days of treatment at the plasma exposure (AUC_{0-24h}) of 57,800 h.ng/mL, although the tumors started to progress after approximately 30 days of treatment in this C1156Y model (Figure 1-2) [internal data].

Similar to some of the patients who progressed on crizotinib while maintaining the ALK translocation but had no secondary mutations in ALK, several crizotinib-resistant H2228 models were found to carry EML4-ALK that had no secondary mutations in ALK (ALK wild type). When LDK378 was tested in one of these ALK wild type crizotinib resistant models, it also demonstrated potent antitumor activity inhibiting tumor growth at 50 mg/kg and causing tumor regression at 100 mg/kg (Figure 1-3). The anti-tumor activity of LDK378 in these models may be related to the higher potency for ALK inhibition as compared to crizotinib. In the clinic, patients likely will harbour tumors with a mix of ALK wild type and ALK mutated cancer cells, especially after progression on crizotinib,

These data support that LDK378 may be clinically active in ALK-rearranged NSCLCs that have become resistant to crizotinib.

[redacted]

Figure 1-2 Anti-tumor activity of LDK378 in a crizotinib-resistant mouse H2228 model with an ALK C1156Y mutation

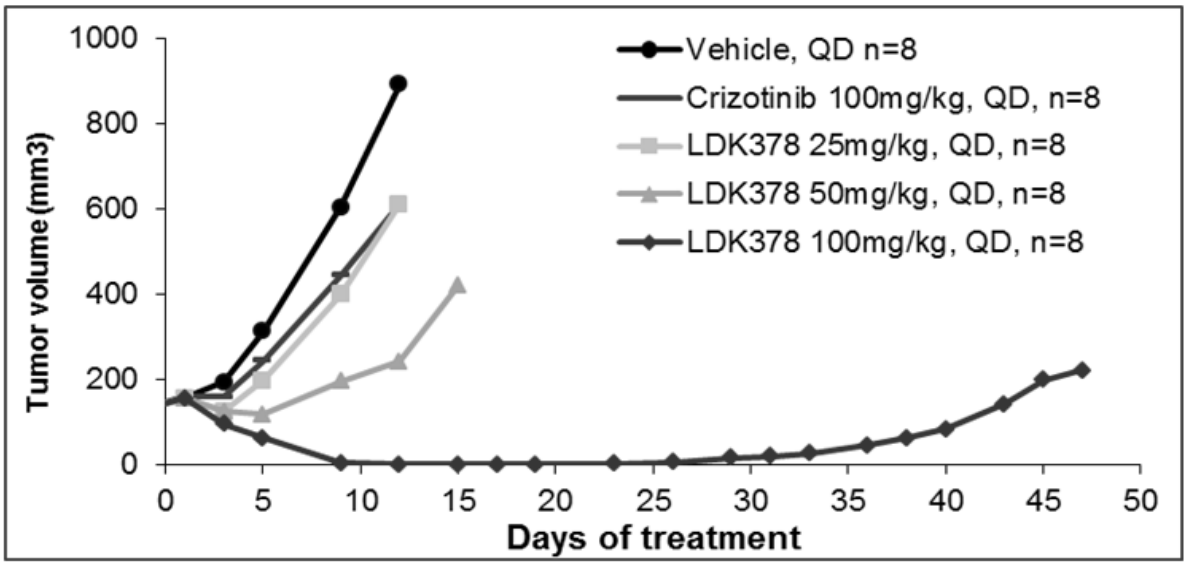
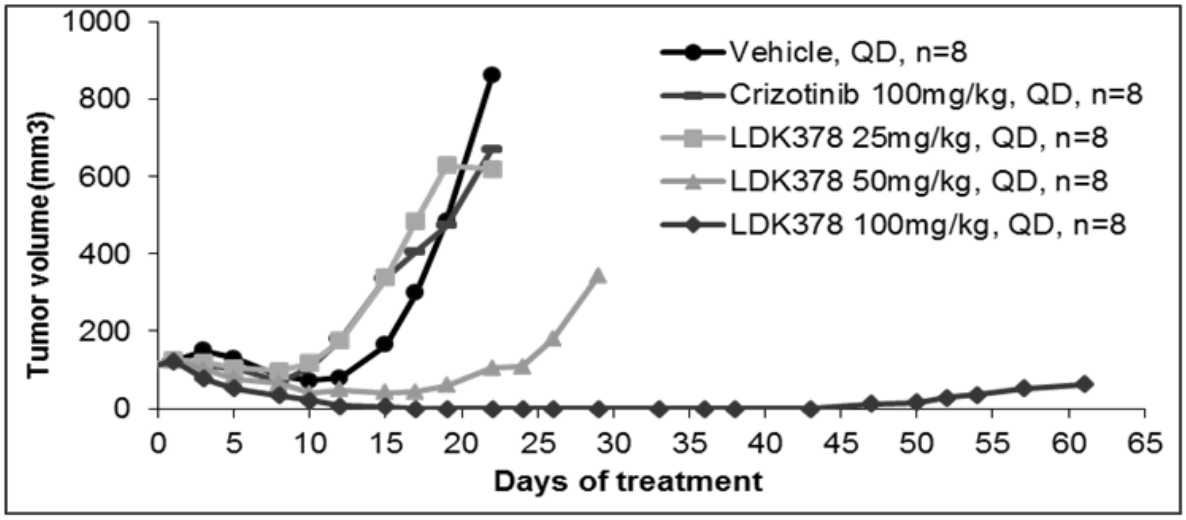


Figure 1-3 Anti-tumor activity of LDK378 in a crizotinib-resistant mouse H2228 model without ALK mutations



1.2.1.1.3 Nonclinical pharmacokinetics (PKs) and metabolism

In general, LDK378 was moderately absorbed in rats (37%) and monkeys (≥40%). Oral bioavailability was complete in fed dogs, suggesting the possible existence of a positive food effect. The formulation used in these bioavailability determinations was a 0.5% methylcellulose suspension except for in the mouse where a solution formulation was used. LDK378 is highly bound to plasma protein (>94%) in all species. Following oral administration of [^{14}C] LDK378 to LEH male rats, radioactivity was widely distributed. The highest tissue exposures were found in intestine wall, uveal tract, pituitary gland, bile, adrenal

[redacted]

cortex, harderian gland, liver, spleen, lymph node, lung, kidney, thyroid, bone marrow, adrenal medulla and pancreas (25- to 710-fold higher exposure relative to blood). Although the brain to blood concentration ratio of drug-related radioactivity was low compared to these other tissues brain-to-blood exposure (AUC_{inf}) ratio of approximately 15%, it was higher than the 3% background associated with brain vasculature at all monitored time points. This indicates that drug-related radioactivity crossed the blood-brain barrier. Unchanged LDK378 was the major component in feces and bile of intact and bile duct-cannulated rats. In the rat, LDK378 underwent oxidation leading to the formation of four oxygenated metabolites (designated as M23.6, M30.6, M35.8, and M33.4). In addition, LDK378 underwent sulfation leading to M36.8 and oxidation followed by sulfation resulting in the presence of M29.5. LDK378 also underwent glucuronidation leading to M26.8 and M27.6. The major metabolite in feces was designated M33.4 (oxygenation) accounting for approximately 7% of the dose. All other metabolites in feces and bile were minor (<5% of the dose). In rats dosed with [^{14}C] LDK378, LDK378 -derived radioactivity was excreted predominantly via the fecal route (>99%), and renal excretion was a minor pathway for excretion (<1%). Fecal excretion was the result of biliary excretion (69%) and gastrointestinal (GI) secretion (31%). Since parent drug was the major component in bile and feces after intravenous (i.v.) administration, enterohepatic circulation may occur.

CYP3A4/5 is the major hepatic enzyme metabolizing LDK378 in a human *in vitro* system. The metabolic drug-drug interaction (DDI) potential of LDK378 as an inhibitor was evaluated using pooled human liver microsomes. Based on the assessment of clinical significance of in vitro results using the appropriate DDI decision tree described in FDA draft DDI guidance 2012 and EMA DDI guideline 2012, at clinically relevant concentrations, LDK378 is unlikely to inhibit CYP1A2, 2B6, 2C8, 2C19 or 2D6. Only CYP2A6, 3A4, 2C9 and possibly CYP2E1 need to be considered as possible victims of in vivo inhibition by LDK378. LDK378 is also a time-dependent CYP3A inhibitor (Ki: 1.47 µM and Kinact: 0.0642 min^{-1}), but shows no apparent time-dependent inhibition of CYP1A2, 2C9 or 2D6 at LDK378 concentrations of up to 50 µM.

LDK378 is likely a P-gp substrate, but not BCRP or MRP2 substrate. It does not inhibit P-gp, BCRP or MRP2 at concentrations up to 1.5 µM *in vitro*.

Kinetic PK/pharmacodynamic modeling was performed in the nude rat H2228 model (constitutively expressing ELM4-ALK gene) and the nude rat Karpas 299 model (expressing NPM-ALK). The minimal pharmacologic dose in humans was estimated to be 100 mg/day for tumor stasis.

1.2.1.1.4 Safety pharmacology and toxicology

LDK378 was evaluated for safety in 2- and 4-week studies in rats and monkeys. The principal toxicity induced by LDK378 was a systemic inflammation characterized by increased neutrophil counts in the peripheral blood and mixed cell/neutrophilic inflammation of the biliopancreatic ducts, pancreas, and/or duodenum. Gastrointestinal toxicity was observed in both species characterized by body weight loss, decreased food consumption, emesis (monkey), diarrhea, and at high doses, by histopathologic lesions including erosion, mucosal inflammation, and foamy macrophages in the duodenal crypts and ampullae of rats and monkeys, respectively. The liver (bile duct) was also affected in both species only at the

[redacted]

highest dose levels studied (100 mg/kg/day in the 2-week studies for both rat and monkeys and 50 and 30 mg/kg/day in the 4-weeks studies in rat and monkeys, respectively), and included increases in liver transaminases in a few animals at high doses, and mixed cell inflammation, erosion and cytoplasmic vacuolation of the bile duct epithelium. The pancreas was a target organ in the rat, but not the monkey, with acinar cell atrophy and mixed cell inflammation noted at middle and high doses. Target organ effects showed partial to complete recovery during the 4-week non-dosing period. No effects in the rat central nervous system or on the respiratory system were observed at single, high doses (100 mg/kg).

LDK378 has potent activity on the hERG channel with an IC50 of 0.4 μc. However, there were no LDK378-related effects in vivo in monkeys at doses as high as 100 mg/kg (human equivalent dose [HED] of 1950 mg).

Preclinical studies (in vitro 3T3 NRU assay, refer to [Investigators Brochure]) indicated a low risk of phototoxicity with use of LDK378. However, a preliminary analysis from an in vivo ultraviolet local lymph node assay (UV LLNA) demonstrated no phototoxic potential with LDK378.

Preclinical studies including an *in vitro* 3T3 NRU assay, and a definitive *in vivo* ultraviolet local lymph node assay (UV LLNA) together demonstrate no phototoxic risk with LDK378 (refer to [Investigators Brochure]).

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety and tolerability

LDK378 is associated with a generally manageable safety profile. For the 255 patients treated at the recommended dose (RD) of 750 mg in the ongoing study CLDK378X2101, the median duration of exposure as of the 31-Oct-2013 cut-off date was 26.9 weeks (range 0.4 to 82.3 weeks). The most common adverse events regardless of study drug relationship (incidence ≥25%) were diarrhea, nausea, vomiting, alanine aminotransferase (ALT) increased, fatigue, abdominal pain, decreased appetite, aspartate aminotransferase (AST) increased, and constipation.

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

[redacted]

Table 1-1 All grades (at least 10%) and grade 3-4 adverse events, regardless of study drug relationship, by preferred term in patients treated in the 750 mg dose group (Data cut-off date: 31-Oct-2013)

	LDK378 750 mg N=255	
	All Grades	Grade 3/4
Preferred term	n (%)	n (%)
Total	**255 (100.0)**	**184 (72.2)**
Diarrhea	219 (85.9)	15 (5.9)
Nausea	205 (80.4)	11 (4.3)
Vomiting	153 (60.0)	10 (3.9)
Alanine Aminotransferase Increased	110 (43.1)	68 (26.7)
Fatigue	102 (40.0)	10 (3.9)
Abdominal Pain	91 (35.7)	3 (1.2)
Decreased Appetite	87 (34.1)	2 (0.8)
Aspartate Aminotransferase Increased	78 (30.6)	21 (8.2)
Constipation	73 (28.6)	0
Cough	62 (24.3)	0
Abdominal Pain Upper	58 (22.7)	2 (0.8)
Dyspnea	47 (18.4)	8 (3.1)
Asthenia	45 (17.6)	2 (0.8)
Blood Alkaline Phosphatase Increased	45 (17.6)	13 (5.1)
Back Pain	43 (16.9)	1 (0.4)
Headache	41 (16.1)	3 (1.2)
Weight Decreased	39 (15.3)	4 (1.6)
Blood Creatinine Increased	39 (15.3)	0
Pyrexia	38 (14.9)	0
Rash	32 (12.5)	0
Insomnia	31 (12.2)	0
Dyspepsia	26 (10.2)	1 (0.4)
Hypokalemia	26 (10.2)	11 (4.3)
Dizziness	26 (10.2)	0

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

Serious adverse events (SAEs) reported in 2% or more of the 255 patients treated at the recommended dose of 750 mg were convulsion, pneumonia, interstitial lung disease (ILD)/pneumonitis, dyspnea, hyperglycemia, and nausea. Fatal adverse reactions occurred in

[redacted]

5% of patients, consisting of: pneumonia (4 patients), respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and sepsis (1 patient each). Adverse events of special interest to be monitored for ceritinib have also been identified and include: hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations). For additional details, refer to [Investigator's Brochure].

As of 29-Apr-2013, 19 patients have been treated with LDK378 in a phase I Japanese study [CLDK378X1101]. Patients have been treated on a once daily schedule at the following dose levels: 300 mg, 450 mg, 600 mg, and 750 mg. A total of 19 patients are evaluable for adverse events. Gastrointestinal toxicities, including nausea, diarrhea and vomiting were the most common adverse events, occurring in 94.7%, 73.7% and 73.7% of patients, respectively. Blood creatinine increased (63.2%), decreased appetite (52.6%), fatigue (36.8%), abdominal pain, constipation, hyperuricaemia (each 26.3%), ALT increased, anaemia, AST increased, headache, neutropenia, pyrexia, rash, rash maculopapular (each 21.1%) were also common. All other adverse events occurred in less than 20% of patients. Grade 3 and 4 adverse events were much less common. ALT increased and tumor pain occurred in two patients. All other grade 3 or 4 events occurred in one patient. During the escalation part of the study two patients experienced dose limiting toxicity (DLT), one at 600 mg qd (lipase increased), and one at 750 mg qd (drug-induced liver injury). The DLTs resolved in all patients, however, one patient discontinued the study due to drug-induced liver injury. Following clinical review by the investigators and Novartis, and assessment of the probability of DLT by BLRM, 750 mg qd was determined to be the MTD. At the 750 mg dose level the probability of overdose (DLT rate $\geq$ 33%) based on the BLRM was 7.3%, which satisfied the overdose criterion of < 25%. Following determination of the MTD in January 2013 the dose expansion phase of the study opened at the 750 mg qd dose level, and accrual to the expansion group is ongoing.

1.2.1.2.2 Clinical efficacy

As of 31-Oct-2013, data from the ongoing Study [CLDK378X2101] demonstrated a high rate of rapid and durable responses with LDK378 in 246 ALK-positive NSCLC patients treated in the 750 mg dose group (RD). The Full Analysis Set (FAS) consisted of all patients with ALK-positive NSCLC in the 750 mg treatment dose group (FAS-NSCLC 750 mg group). In these patients the Overall Response Rate (ORR) was 58.5% (95% CI: 52.1, 64.8) based on investigator assessment (Table 1-2). Among the 144 ALK-positive NSCLC patients with a confirmed Complete Response (CR) or Partial Response (PR) based on investigator assessment, the median time to response was short at 6.1 weeks (range: 3.0 to 24.1) and 86.1% of the patients achieved a response within 12 weeks. The estimated median Duration of Response (DOR) based on investigator assessment was long at 9.69 months (95% CI: 7.00, 11.40)

LDK378 showed this level of high anti-cancer activity regardless of prior ALK inhibitor status (i.e., whether or not the patient received previous treatment with an ALK inhibitor). A high ORR of 54.6% and 66.3% was observed in patients treated with a prior ALK inhibitor and in ALK inhibitor naïve patients, respectively, by investigator assessment (Table 1-2). Rapid responses were observed in patients regardless of prior ALK inhibitor status, 6.1 weeks

(range: 4.6 to 24.1) in patients treated with a prior ALK inhibitor and 6.1 weeks (range: 3.0 to 24.1) in ALK inhibitor naïve patients. Further, the estimated median DOR was 7.39 months (95% CI: 5.42, 10.12) in patients treated with a prior ALK inhibitor andthe median DOR was not reached (95% CI: 9.59, NE) in ALK inhibitor naïve patients, however the 12-month DOR rate was 65.2% (95% CI: 46.4, 78.8) The estimated median PFS was 6.90 months (95% CI: 5.39, 8.41) in patients treated with a prior ALK inhibitor, while the median PFS was not reached in ALK inhibitor naïve patients (95% CI: 8.31, NE) Finally, LDK378 demonstrated activity in patients with brain metastases at baseline. Among the 98 patients with brain metastasis who had received prior ALK-inhibitor treatment, the ORR was 50% (95% CI: 39.7, 60.3), DOR was 6.9 months (95% CI: 4.8, 8.5), and PFS was 6.7 months (95% CI: 4.9, 8.4). For additional details, refer to the [Investigator's Brochure]. The analysis by the BIRC assessment was similar to the analysis by the investigator assessment.

Table 1-2 Summary of best overall response based on investigator assessment in NSCLC patients in the 750 mg dose group, by prior ALK inhibitor status (Full Analysis Set NSCLC 750 mg) (Cut-off date: 31-Oct-2013)

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

This table presents data for all patients with ALK-positive NSCLC in the 750 mg treatment dose group, **FAS-NSCLC 750 mg group**
Best overall response is based on investigator's assessment of disease status using RECIST 1.0 criteria
CR and PR are confirmed by repeat assessments performed not less than 4 weeks after the criteria for response are first met.
Exact binomial 95% Confidence Interval

1.2.1.2.3 Clinical pharmacodynamics

Data are not available from the ongoing clinical study.

1.2.1.2.4 Clinical pharmacokinetics

In adult patients with tumors characterized by genetic abnormalities in ALK [redacted] and in healthy volunteers [redacted], [redacted] and [redacted], single-dose pharmacokinetics (PK) of LDK378 in humans has the following features: (1) LDK378 was slowly absorbed, with median peak plasma concentration occurring at approximately 4 to 6 h in patients, and approximately 6 to 8 h in healthy subjects. Following Cmax, LDK378 concentrations declined in a mono-exponential manner. The geometric mean apparent terminal half-life ranged from 31 to 41 h across the

[redacted]

400 to 750 mg dose groups in patients and 36 to 48 h across the 450 to 750 mg dose groups in healthy subjects. (2) Cmax and AUClast increased dose-proportionally following single oral administration of LDK378 across the 50 to 750 mg dose groups in patients. (3) moderate to high variability in LDK378 PK parameters has been observed in both healthy subjects and patients. Following single oral doses of 450 to 750 mg in healthy subjects when LDK378 was given alone, the inter-subject variability (geometric mean coefficient of variation; CV% range) was 42-74% and 35-72% for AUClast and Cmax, respectively. The corresponding values in patients were 93% and 87% following single oral doses of 50 to 750 mg based on a model developed for dose proportionality analysis.

Multiple-dose PK of LDK378 following repeated daily oral dosing in patients has the following features: (1) following LDK378 750 mg once daily dosing, steady-state was reached by approximately 15 days with a geometric mean accumulation ratio of 6.2 after 3 weeks: (2) LDK378 demonstrated nonlinear PK over time, as indicated by the observed difference in apparent clearance (CL/F) between single-dose (88.5 L/h at 750 mg) and steady-state at Cycle 2 Day 1 (33.2 L/h at 750 mg). As LDK378 is a substrate as well as a time-dependent inhibitor of CYP3A, it is likely that this PK nonlinearity could be attributed to auto-inhibition of LDK378. In contrast with single dose data, Ctrough on Cycle 2 Day 1 after repeated daily dosing increased with dose in a greater than dose-proportional manner.

In the human ADME study [redacted], the majority of the radioactivity dose in humans was eliminated in the feces (mean: 91.0%) with only a minor amount eliminated in the urine (mean: 1.3%) following a single oral dose of 750 mg of [14C]LDK378 to healthy male subjects. The mean percentage of the dose eliminated in the feces as unchanged LDK378 was 68.0% while all the metabolites were present at low levels, with no individual metabolite contributing greater than 2.3% to the radioactivity AUC. Hepatic metabolism and potentially biliary excretion and GI secretion all contribute to LDK378 elimination in humans while the kidney appears to play a negligible role. The primary biotransformation pathways of LDK378 that were observed included mono-oxygenation, O-dealkylation, and N-formylation. Unchanged LDK378 was the most abundant drug-related component found in both the plasma and excreta.

CYP3A was identified as the major CYP isozyme responsible for the metabolism of LDK378 in humans. An inhibition DDI study conducted in healthy volunteers indicated that ketoconazole (200 mg bid for 14 days), a strong CYP3A inhibitor, increased the Cmax and AUCinf of a single 450 mg oral dose of LDK378 by 1.2-fold and 2.9-fold, respectively, compared with LDK378 alone [redacted]. These results demonstrated that concurrent use of strong CYP3A inhibitors may markedly increase LDK378 exposure and should be avoided. An induction DDI study conducted in healthy volunteers indicated that rifampin (600 mg daily for 14 days), a strong CYP3A inducer, decreased the Cmax and AUCinf of a single 750 mg oral dose of LDK378 by 44% and 70%, respectively, compared with LDK378 alone [Study LDK378A2106]. These results demonstrated that concurrent use of strong CYP3A inducers may markedly decrease LDK378 exposure and should be avoided.

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

[redacted]

To further clarify if low fat content has an impact on the extent of LDK378 absorption, a food effect assessment with a very low-fat light snack (containing approximately 100-300 calories and 1.5 grams of fat) was also explored in a relative bioavailability study conducted in healthy subjects [redacted]. PK data from the light snack cohort showed that when a single 750 mg oral dose of ceritinib was administered with a light snack, the Cmax and AUCinf increased by 45% and 54% respectively, compared to the fasted condition. This magnitude of increase is similar to that caused by a low-fat meal as described in Study [redacted], suggesting that even a very low-fat meal could lead to a clinically meaningful LDK378 exposure increase.

1.3 Risk and Benefits

Overall benefit-risk

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

Efficacy

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

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

The efficacy of ceritinib seen in Study [redacted] is highly encouraging in heavily pretreated patients with advanced disease, high tumor burden (including a high proportion of brain metastases at baseline), limited available therapeutic options, and dismal prognoses

[redacted]

following prior ALK-targeted therapies, where the only options are chemotherapy and best supportive care.

ALK inhibitor naïve patients: As of 31-Oct-2013, based on an independent review of tumor assessments, the response rate in ALK inhibitor naïve NSCLC patients was 61.0% (95% CI: 49.2 - 72.0) in Study [redacted]. The median DOR was not evaluable for treatment-naïve patients. The median PFS for ceritinib in ALK-inhibitor naïve patients was not evaluable (95% CI: 13.7 - NE) as the majority of patients were ongoing without an event at the time of the data cut-off.

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

Safety

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

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

Risk management during study conduct

In order to manage the risks associated with ceritinib treatment, specific dose modifications and stopping rules during study conduct are described in the protocol. For patients who do not tolerate the initial protocol-specified dose, dose adjustments are provided in order to allow the patients to continue the study treatment (Section 6.3 and Table 6-2). Patients whose treatment is temporarily interrupted or permanently discontinued due to a study drug related AE or an abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

In addition, a thorough post-treatment safety follow-up is included (Section 7.1.7.2). Patients may voluntarily withdraw from study treatment at any time or on the advice of the investigator if he/she believes that continuation would be detrimental to the patient's well-being. When the patient discontinues from study treatment, an End of Treatment (EOT) visit must be performed as soon as possible and within 7 days of the last dose of ceritinib. Patients will also be contacted for the safety follow-up 30 days after their last dose of ceritinib to determine if they have experienced any new AEs and/or to follow resolution of ongoing AEs.

[redacted]

Detailed information on allowed and prohibited concomitant medications is provided in Section 6.4. *In vitro* drug metabolism studies show that the metabolism of ceritinib is mediated by CYP3A4/5. Appendix 1 contains several tables listing medications that are prohibited, permitted or to be used with caution during treatment with ceritinib. Prohibited medications should be discontinued at least 1 week prior to the start of treatment with ceritinib (see exclusion criteria #11).

Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, are extensively described in Section 6.2.4.

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

- Hepatotoxicity: Hepatotoxicity, as defined by TB > 2xULN and ALT and/or AST > 3xULN and ALP < 2xULN, has been observed in <1% of patients treated with ceritinibIncreases to grade 3 or 4 ALT elevations were observed in 25% of patients receiving ceritinib. Concurrent elevations in ALT >3xULN and total bilirubin >2xULN, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of ceritinib. Patients will be closely monitored by regular laboratory testing and related signs and symptoms. Risk to patients will also be minimized by restricting study enrollment to subjects with laboratory values for AST, ALT, ALP and bilirubin below certain thresholds (see inclusion criteria #7).
- Interstitial lung disease/pneumonitis: severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with ceritinib in clinical studies. Most cases improved or resolved with interruption of ceritinib. Patients will be monitored for symptoms such as shortness of breath, cough or fever. Risk to patients will be minimized by excluding from study enrollment any patient with a history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention) (see exclusion criteria #19).
- QT interval prolongation: QTc prolongation has been observed in clinical studies in patients treated with ceritinib, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death. A pharmacokinetic analysis suggested that ceritinib causes concentration-dependent increases in QTc. Repeated ECG tracings will be performed throughout the study to closely monitor cardiovascular safety. Risk to patients will also be minimized by excluding from study enrollment those patients with clinically significant, uncontrolled heart disease and/or a recent cardiac event (within 6 months), including a corrected QT (QTcF) > 470 ms using Fridericia's correction on the screening ECG (see exclusion criteria #8).
- Bradycardia: asymptomatic cases of bradycardia have been observed in patients treated with ceritinib in clinical studies. Repeated ECG tracings will be performed throughout the study to closely monitor cardiovascular safety. Risk will also be minimized by monitoring concomitant use of other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Heart rate and blood pressure will also be monitored regularly during the study.
- Hyperglycemia: events of hyperglycemia (all grades) have been reported in less than 10% of patients treated with ceritinib in clinical studies; 5% of patients reported a grade 3/4

[redacted]

event. The risk of hyperglycemia was higher in patients with diabetes mellitus and/or concurrent steroid use. Patients will be closely monitored throughout the study for any signs and symptoms related to elevated blood glucose levels. Risk will be minimized by including subjects with fasting plasma glucose levels ≤ 200 mg/dL (≤ 11.1 mmol/L) at screening (see inclusion #7).

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

Conclusion

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

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

2 Rationale

2.1 Study rationale and purpose

ALK rearrangement is a relatively rare event in NSCLC with a frequency of just 2-8% that results in aberrant ALK activation. ALK fusion proteins possess potent oncogenic activity both in vitro and in vivo. In these patients, ALK rearrangements serve as a key and strong oncogenic driver for NSCLC and represent a critical therapeutic target susceptible to ALK kinase inhibition by small-molecule inhibitors that target ALK, like crizotinib.

Currently, crizotinib is the only drug that is approved specifically for this subset of patients with ALK-positive NSCLC. Nevertheless, 40-50% of patients fail to achieve a response and a high proportion of patients (including the responders) will experience tumor progression within one year of crizotinib treatment as shown by a recently presented phase III trial of crizotinib in second line ALK-positive patients (Shaw et al 2013). To date, following

[redacted]

progression on crizotinib, these patients have no effective ALK-targeted treatment options. Since ALK aberrant activation remains the key oncogenic driver in these tumors, novel ALK targeted therapies with activity against ALK-positive NSCLC that have progressed after crizotinib are needed.

[redacted]

As of 31-Oct-2013, data from the ongoing Study [redacted] demonstrated a high rate of rapid and durable responses with LDK378 in 246 ALK-positive NSCLC patients treated in the 750 mg dose group. In these patients the ORR was 58.5% (95% CI: 52.1, 64.8) based on investigator assessment. A high ORR of 54.6% and 66.3% was observed in patients treated with a prior ALK inhibitor and the ALK inhibitor naïve patients, respectively. The estimated median PFS was 6.90 months (95% CI: 5.39, 8.41) in patients treated with a prior ALK inhibitor, while the median PFS was not reached in ALK inhibitor naïve patients (95% CI: 8.31, NE). Further, the estimated median DOR was 7.39 months (95% CI: 5.42, 10.12) in patients treated with a prior ALK inhibitor, the median DOR was not reached (95% CI: 9.59, NE) for the ALK inhibitor naïve patients, however the 12-month DOR rate was 65.2% (95% CI: 46.4, 78.8).

Therefore, these data provided the rationale for the ongoing global phase II [redacted] and phase III study [redacted] in ALK-positive NSCLC failing crizotinib. The purpose of this phase I/II study is to characterize the PK, safety and efficacy data of LDK378 when used as a single agent in Chinese ALK-rearranged advanced NSCLC patients who have been pretreated with crizotinib and have no available ALK-targeted therapy. This study will support LDK378 registration in China.

2.2 Rationale for the study design

This is a phase I/II, open-label, multi-center study to assess PK, safety, tolerability and efficacy of LDK378 in Chinese adult patients with ALK-rearranged locally advanced or metastatic NSCLC who have been previously treated with crizotinib. The study includes a phase I component for the first 15 patients (5 day PK run-in period) and a phase II component for all the patient with continuous dosing (see below). Patients must have progressive disease during or after crizotinib treatment whether or not they have been previously treated with cytotoxic chemotherapy. These patients do not have any available ALK-targeted treatment option to date. Data from the ongoing phase I study [redacted] suggest that advanced NSCLC patients respond to LDK378 after failing crizotinib.

Indeed two single arm studies, the phase I study [redacted] and a phase II study [redacted] will support LDK378 global registration in this indication. Therefore, it is reasonable to use a single arm study in Chinese patients to support registration of LDK378 in NSCLC patients that progress after crizotinib in China.

Two phase I studies, the [redacted] global study and [redacted] Japanese study, have already determined the MTD/RP2D (recommended phase 2 dose) for LDK378 single agent to be 750 mg/day. However as required by the Health Authority in China, a

[redacted]

dedicated study is necessary to assess pharmacokinetics profile in Chinese patients. This phase I/II single-arm study will be conducted to meet China registration requirements and to characterize the pharmacokinetics, safety and efficacy of LDK378 in Chinese patients with ALK-rearranged NSCLC treated with crizotinib.

The primary objective of this study is to characterize PK profile, safety and tolerability in this population. The primary measure of PK profile is plasma concentration-time profiles of LDK378 and PK parameters, including but not limited to AUClast, AUC0-24h, Cmax, Tmax, terminal T1/2, effective T1/2, acc, Racc, CL/F and Vz/F, as appropriate. Based on the PK data during PK run-in period from the study [redacted], LDK378 has an apparent terminal half-life of approximately 36 hours, which could lead to drug accumulation following once daily dosing. Therefore, to characterize the PK profile following a single dose in Chinese patients, a 5-day PK run-in period is designed as the phase I component of the study prior to a treatment period of continuous daily dosing for all enrolled patients (phase II component). Safety will be measured in terms of type, incidence, and severity of adverse events and serious adverse events; changes from baseline in vital signs, laboratory test results and ECGs, severity of adverse events will be assessed based upon CTCAE v.4.03.

The key secondary objective is to evaluate anti-tumor activity of LDK378 in this population. The primary measure of antitumor activity is the overall response rate (ORR) according to RECIST criteria 1.1 and will be estimated based on investigator assessment. ORR is an appropriate endpoint that can be adequately assessed in the context of this single arm trial. A high ORR may predict clinical benefit in this rare population of patients with ALK-rearranged NSCLC that has progressed during or after crizotinib therapy and for whom there is no available ALK-targeted therapy. Data on ORR will be supplemented with data on duration of response (DOR) and time to response (TTR).

The study will also assess progression-free survival (PFS), overall survival (OS) and [redacted]. These endpoints are considered to be important supportive endpoints to better assess the potential clinical benefit of LDK378.

2.3 Rationale for dose and regimen selection

In the dose-escalation phase of Study [redacted], 59 patients were treated at dose levels of 50 to 750 mg. Eight Dose Limiting Toxicities (DLTs) at Cycle 1 were observed in 6 patients:

[redacted]

- At 400 mg: grade 3 hypophosphatemia in one patient, and grade 3 transaminase increased evolving from grade 2 ALT increased in one patient.
- At 600 mg: grade 3 diarrhea and grade 3 dehydration in one patient each.
- At 750 mg: grade 3 diarrhea with grade 3 vomiting in one patient and intolerable grade 2 diarrhea in one patient.

Based on the Bayesian logistic regression model (BLRM) used to guide dose escalation, the probability of overdose (>25% probability that the DLT rate ≥ 33%) at Cycle 1 was 3.3% at the 750 mg dose level. However, during the dose-escalation discussion between the investigators and the sponsor, further dose escalation was considered to be medically inappropriate due to the increasing frequency of persistent grade 1-2 nausea, vomiting and diarrhea, and the occasional occurrence of grade 3-4 ALT and AST increases with prolongued treatment. Further confirmation of the 750 mg dose as the appropriate Maximum Tolerated Dose (MTD) came from the incidence of DLTs in Cycle 1 in the first 10 patients treated at this dose in the expansion phase of the study. There were no first-cycle DLTs in these 10 patients, thus confirming the 750 mg dose as a safe MTD and RD [Study X2101-Section 11.3].

Among the different doses tested, the RD for the expansion phase was determined to be 750 mg, the highest dose evaluated. The following safety and efficacy considerations were taken into account:

- Safety data indicated that LDK378 is generally well tolerated at 750 mg for multiple cycles of therapy, without evident difference in the frequency of AEs versus immediate lower doses (400-700 mg)
- Although preliminary efficacy data indicated that tumor responses are observed consistently at doses of 400 mg and above, the response duration appeared to be shorter at the lower doses. Nonclinical data from ALK-positive NSCLC xenograft models indicated that LDK378 should be dosed at the MTD to maximize efficacy, in particular against crizotinib resistant tumor models.

Demographic data and PK parameters were compared between non-Asian patients and Asian patients in [redacted]. Concerning demographic characteristics, the median baseline body weight of the Asian population was 60 kg, which was 17% lower than that of the non-Asian population of 72 kg. Ethnic sensitivity analysis indicated that after three weeks of daily dosing at 750 mg, Cmax and AUC0-24 were only 1.26-fold (1180 ng/mL vs. 938 ng/mL) and 1.04-fold (23100 ng*h/mL vs. 22200 ng*h/mL) higher in the Asian population compared to those seen in the non-Asian population, respectively. The accumulation ratio at steady-state obtained in the Asians and non-Asians were also similar (Asians: 5.89 vs. non-Asians: 6.46). Another phase I clinical trial [redacted] is ongoing in Japanese patients (See Section 1.2.1.2.1) The PK exposure results in the Japanese patients determined during escalation phase were within the range of the results determined in the non-Japanese patients from [redacted]. Overall, there was no marked ethnic difference (≤ 30% difference) in PK parameters between Asian and All others groups.

Therefore, considering the pre-clinical data (e.g. higher anti-tumor activity with higher doses), available PK data across Asian and non-Asian population and clinical safety and efficacy data (good tolerability and efficacy of 750 mg), the dose of LDK378 750 mg QD is anticipated to

[redacted]

be tolerable and efficacious in Chinese patients. In study [CLDK378A2109], LDK378 will be administered orally, once daily at a dose of 750 mg, continuously in 28-day cycles. A single oral dose of LDK378 at 750 mg will be given to the first enrolled 15 patients during the PK run-in period (5 days) prior to initiating study drug on Cycle 1 Day 1.

[redacted]

3 Objectives and endpoints

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

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		Refer to Section 10.4
To characterize the pharmacokinetics profile of LDK378 in Chinese adult patients with ALK-rearranged NSCLC previously treated with crizotinib following single and multiple daily oral dose of LDK378 To assess the safety and tolerability of LDK378 after consecutive 750 mg once daily dose in Chinese adult patients with ALK-positive NSCLC	Plasma concentration of LDK378 and PK parameters, including but not limited to AUClast, AUC0-24h, AUCinf, Cmax, Tmax, Lambda_z terminal T1/2, T1/2,acc, Racc, CL/F (or CLss/F at steady state) and Vz/F, as appropriate Adverse events, vital signs, ECGs and laboratory abnormalities	
Key secondary		Refer to Section 10.5.1
To demonstrate the antitumor activity of LDK378, as measured by overall response rate (ORR) to LDK378 by investigator assessment	ORR per RECIST 1.1 calculated as the proportion of patients with a best overall response defined as complete response (CR) or partial response (PR) by investigator assessment	
Other secondary		Refer to Section 10.5.2
To evaluate response related endpoints as assessed by investigator: 1. Duration of response (DOR) 2. Disease control rate (DCR) 3. Time to Response (TTR) 4. Overall intracranial response rate (OIRR) 5. Progression-free survival (PFS) 6. Overall survival (OS) ORR and OIRR will also be evaluated as assessed by BIRC.	The following endpoints will be evaluated by investigator assessment per RECIST 1.1: 1. DOR, calculated as the time from the date of the first documented CR or PR to the first documented progression or all cause death 2. DCR, calculated as the proportion of patients with best overall response of CR, PR, or SD 3. TTR, calculated as the time from first dose of LDK378 to first documented response (CR+PR) 4. OIRR calculated as the ORR (CR+PR) of lesions in the brain for patients who have measureable disease in the brain at baseline 5. PFS, defined as time from first dose of LDK378 to progression or death due to any cause 6. OS, defined as time from first dose of LDK378 to death due to any cause ORR and OIRR as assessed by BIRC will be the basis of supportive	

[redacted]

[redacted]

[redacted]

4 Study design

4.1 Description of study design

This is a phase I/II, open-label, multi-center study in which the PK, safety, tolerability and efficacy of LDK378 will be assessed in adult Chinese patients with locally advanced or metastatic NSCLC harboring a confirmed ALK rearrangement, defined as positive using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria) or positive as assessed by the CFDA approved immunohistochemistry (IHC) test (Ventana Medical Systems, Inc) using rabbit monoclonal primary antibody assay (D5F3) and associated scoring algorithm.

If documentation of ALK rearrangement is not available as described above, a test to confirm ALK rearrangement must be performed using an archival tumor obtained at or since the time of diagnosis or a new tumor biopsy obtained prior to the first LDK378 dose. The test will be performed at a Novartis designated central laboratory (by IHC test using rabbit monoclonal primary antibody assay (D5F3), Ventana Medical Systems, Inc). Patients must wait for the result of the ALK rearrangement status before initiating treatment with LDK378.

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 with locally advanced or metastatic NSCLC which harbor ALK -rearrangement will be enrolled in the study. Patients will have a screening period, a treatment period, an end of treatment (EOT) assessment and a follow up period.

The study begins with a screening period, up to and including 28 days prior to the first dose of LDK378, to assess eligibility.

The first 15 enrolled patients will enter a 5-day PK run-in period during the phase I component of this study. The phase II component of the study will start on Cycle 1 Day 1 for all enrolled patients.

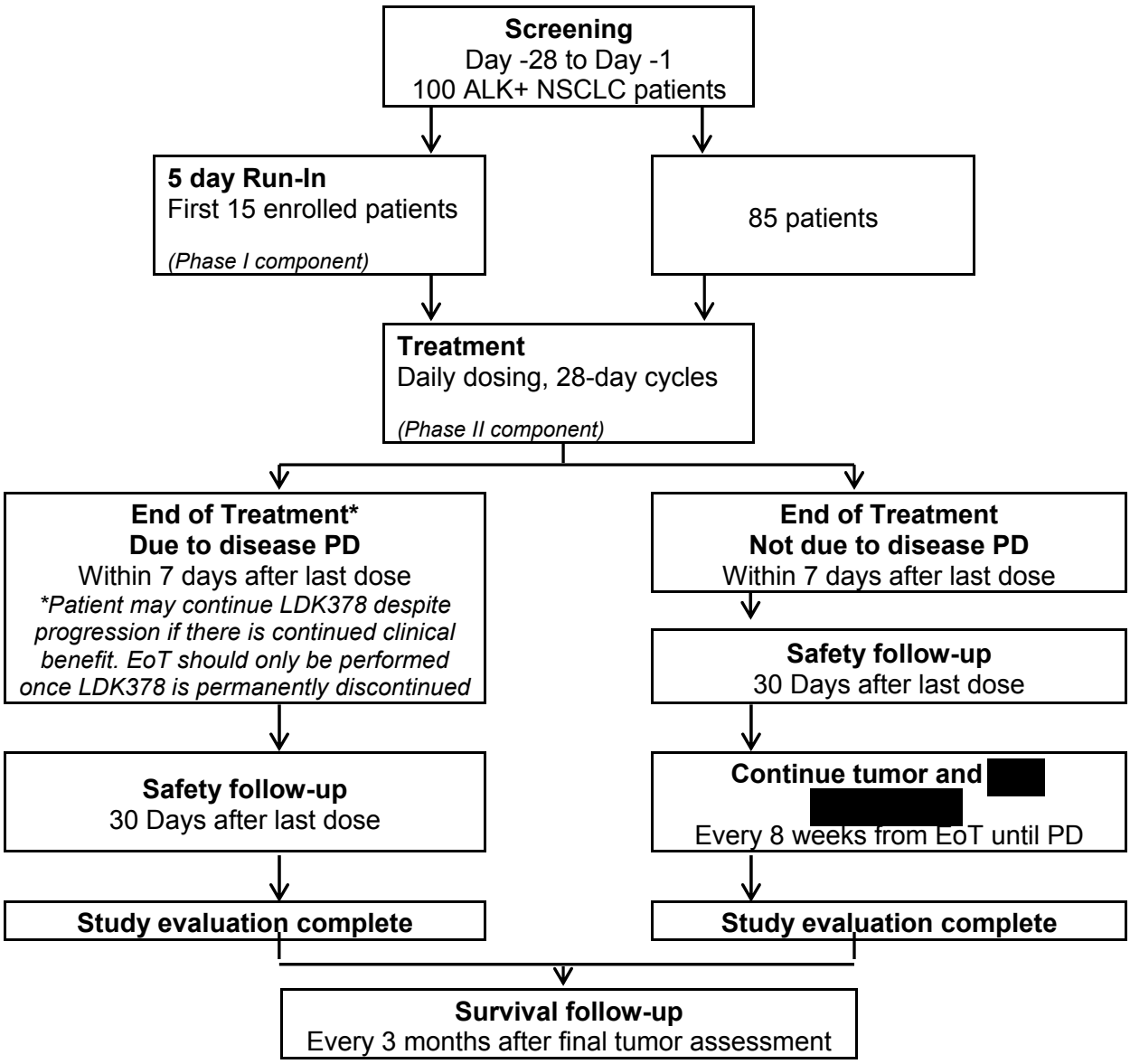
The first 15 patients to be enrolled in the phase I component of the study will have PK sampling over 120-hour during the 5-day PK run-in period following a single oral dose at 750 mg. This will be done in order to characterize the PK profile, safety and tolerability of LDK378 after single dosing in this population.

After the PK run-in period, the treatment period for the first 15 patients will start on Cycle 1 Day 1 in which LDK378 will be given as continuous daily oral dosing at 750 mg QD in 28-day cycles. Apart from these 15 patients, the rest of the enrolled patients will start treatment with LDK378 at 750 mg QD on Cycle 1 Day 1 in 28-day cycles as phase II component of the study.

Data from all patients entering the 28-day cycles treatment period will be used to characterize the PK profile, safety and tolerability of LDK378 as continuous 750 mg once daily dose as well as to demonstrate the antitumor activity of LDK378 as measured by ORR by investigator assessment.

[redacted]

Figure 4-1 Study Design



Patients will take LDK378 once daily, at approximately the same time each day in the morning. On days when a PK sample is obtained, the patient will take LDK378 during the clinic visit as instructed by the study staff. Treatment with LDK378 will continue until the patient experiences unacceptable toxicity that precludes further treatment, discontinues treatment at the discretion of the patient or investigator, starts a new anti-cancer therapy or dies. Clinical and laboratory assessments will be performed as described in Section 7. If the patient experiences RECIST-defined progressive disease (PD) on LDK378 as assessed by the investigator, treatment with the study drug may be continued if, in the judgment of the investigator, there is still evidence of clinical benefit. These patients will be counted as PD for ORR, DOR, DCR and PFS calculations.

[redacted]

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 PD by investigator assessment, withdrawal of consent for further follow-up, loss to follow-up or death. This schedule of tumor assessment must continue regardless of dose interruptions. In 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.

When the patient discontinues from study treatment an End of Treatment (EOT) visit must be performed as soon as possible and within 7 days of the last dose of LDK378. Patients will be contacted for the safety follow-up 30 days after their last dose of LDK378 to determine if they have experienced any new AEs and/or to follow resolution of ongoing AEs.

Following the cessation of tumor follow-up assessments, patients will be contacted every 3 months to determine whether the patient has died and/or whether the patient started any other antineoplastic therapies since discontinuing study treatment. Patients do not need to visit the clinic during the survival follow-up.

4.2 Timing of interim analyses and design adaptations

An interim analysis will be performed after the first 30 patients enrolled have completed at least 16 weeks (4 cycles) of treatment with LDK378 or have discontinued earlier. The interim analysis will focus on full pharmacokinetics profile, safety and preliminary efficacy data. See also Section 10.8.

4.3 Definition of end of the study

The primary data analysis will be performed after all patients have undergone at least 24 weeks (6 cycles) of treatment with LDK378 or have discontinued earlier. At this time, the primary clinical study report (CSR) will be produced. Following the primary analysis time point, the study will remain open. Patients still being followed on the study, either still on treatment, efficacy follow up post-treatment discontinuation in the absence of PD, or in survival follow up, will continue as per the schedule of assessments.

The study will end once at least 75% of patients have died, have been lost to follow-up or have withdrawn consent for survival follow-up, The final analysis of study data will be conducted at the end of the study. All available data from all patients up to this cutoff date will be analyzed.

At the end of study (EOS), the patients who are still receiving treatment with LDK378 because they have continuing CR, PR or SD or because they are deriving clinical benefit in the opinion of the investigator despite having a RECIST 1.1 defined progressive disease will be offered enrollment into a separate protocol. In this protocol, Novartis will continue to supply LDK378 to patients who may benefit from continued treatment as per the Investigator's opinion and safety will be monitored and reported to Health Authorities per regulatory requirements. Prior to the end of the current study ([CLDK378A2109]), the separate protocol will be submitted to Health Authorities and IRBs involved in the current study.

[redacted]

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this occur, the patient should be seen as soon as possible and the same assessments as for a discontinued or prematurely withdrawn patient as described in Section 7 should be performed. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

5 Population

5.1 Patient population

This study of LDK378 will be conducted in Chinese adult patients with ALK-rearranged locally advanced or metastatic NSCLC that has progressed during or after crizotinib treatment whether or not previously treated with cytotoxic chemotherapy.

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

Patients enrolled in this study are not permitted to participate in any additional parallel investigational drug or device studies while on treatment. Rescreening will not be allowed.

However, laboratory parameters may be retested within the 28-day screening period for an individual patient if such parameters meet an exclusion criterion when initially tested.

5.2 Inclusion criteria

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

1. Histologically or cytologically confirmed diagnosis of NSCLC, that carries an ALK rearrangement defined as positive using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria) or positive as assessed by the CFDA approved immunohistochemistry (IHC) test (Ventana Medical Systems, Inc) using rabbit monoclonal primary antibody assay (D5F3) and associated scoring algorithm. If documentation of ALK rearrangement is not available as described above, a test to confirm ALK rearrangement must be performed using an archival tumor obtained at or since the time of diagnosis or a new tumor biopsy obtained prior to the first LDK378 dose. The test will be performed at a Novartis designated central laboratory (by IHC test using rabbit monoclonal primary antibody assay (D5F3), Ventana Medical Systems, Inc). Patients must wait for the result of the ALK rearrangement status before initiating treatment with LDK378.
2. Age 18 years or older at the time of informed consent.

[redacted]

3. Patients must have stage IIIB or IV NSCLC at the time of study entry and have had progressive disease during or after crizotinib treatment whether or not previously treated with cytotoxic chemotherapy. If treated with chemotherapy, maximum 2 lines are allowed.
   - Patients must have progressive disease at study entry. Patients are not eligible if crizotinib was discontinued due to toxicity.
   - Patients must have received their last dose of crizotinib ≥ 1 week prior to the first dose of LDK378 and recovered from crizotinib toxicities (as defined in inclusion criteria #4)
   - Prior targeted therapies will not count as a line of cytotoxic chemotherapy (i.e. patients may have received prior treatment with these drugs excluding ALK-inhibitors – See exclusion criteria # 6).
   - (Neo-) adjuvant cytotoxic chemotherapy will count as one prior line of treatment if relapse occurred within 12 months from the end of the adjuvant cytotoxic chemotherapy
   - Note: A cytotoxic chemotherapy line in locally advanced disease is defined as an anticancer regimen that contains at least 1 cytotoxic chemotherapy agent and is given for at least 21 days or more. If a cytotoxic chemotherapy regimen was discontinued for a reason other than disease progression and lasted less than 21 days, then this regimen does not count as a prior line of chemotherapy
4. Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 2 (CTCAE v 4.03). The exception to this criterion is for patients with grade 2 nausea/vomiting and/or grade 2 diarrhea despite optimal supportive therapy who will not be allowed to participate in the study. Patients with any grade of alopecia are allowed to enter the study.
5. Patients must meet the following laboratory values at the screening visit:
   - WBC count ≥ 4.0 x 10^9 /L
   - Absolute Neutrophil Count ≥ 1.5 x 10^9/L
   - Platelets ≥ 100 x 10^9/L
   - Hemoglobin (Hgb) ≥ 9 g/dL
   - Serum creatinine < 1.5 mg/dL and /or calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 30 mL/min
   - Total bilirubin < 1.5 x ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin < 3.0 x ULN or direct bilirubin < 1.5 x ULN
   - Aspartate transaminase (AST) < 2.5 x ULN, except for patients with liver metastasis, who are only included if AST < 5 x ULN
   - Alanine transaminase (ALT) < 2.5 x ULN, except for patients with liver metastasis, who are only included if ALT < 5 x ULN
   - Alkaline phosphatase (ALP) < 5.0 x ULN

[redacted]

6. Patient must have the following laboratory values WNL (within normal limits) or corrected to within normal limits with supplements during screening:
   - Potassium
   - Magnesium
   - Phosphorus
   - Total calcium (corrected for serum albumin)
7. Life expectancy ≥ 12 weeks.
8. World Health Organization (WHO) performance status 0-2.
9. At least one measurable lesion as defined by RECIST 1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the irradiation.
10. Written informed consent for the main study must be obtained prior to any screening procedures. If consent cannot be expressed in writing, it must be formally documented and witnessed, ideally via an independent trusted witness.
11. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study procedures.

5.3 Exclusion criteria

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

1. Patients with known hypersensitivity to any of the excipients of LDK378 (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate).
2. Patients with symptomatic central nervous system (CNS) metastases who are neurologically unstable or have required increasing doses of steroids within the 2 weeks prior to study entry to manage CNS symptoms.
3. History of carcinomatous meningitis.
4. Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
5. Patient has clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months), such as:
   - Unstable angina within 6 months prior to screening
   - Myocardial infarction within 6 months prior to screening
   - History of documented congestive heart failure (New York Heart Association functional classification III-IV)
   - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without antihypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening
   - Ventricular arrhythmias
   - Supraventricular and nodal arrhythmias not controlled with medication

[redacted]

- Other cardiac arrhythmia not controlled with medication
- Corrected QT (QTc) > 470 msec using Fredericia correction (QTcF) (QTcF = $QT/RR^{1/3}$) on the screening ECG

6. Prior therapy with other investigational ALK inhibitors (only prior treatment with crizotinib is allowed).
7. Patients who have received thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment is allowed.
8. Major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within 4 weeks prior (2 weeks for resection of brain metastases) to starting study drug or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study ≥1 week after the procedure.
9. Patients receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 1 week prior to the start of treatment with LDK378 and for the duration of the study (see Appendix I):
   - Strong inhibitors or strong inducers of CYP3A4/5
   - Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5, and/or CYP2C9
   - Medication with a known risk of prolonging the QT interval or inducing Torsades de Pointes
10. Impairment of GI function or GI disease that may significantly alter the absorption of LDK378 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
11. Patients who are currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants.
12. Patients receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms, (other than CNS-related), dose must have been stabilized (or decreasing) for at least 5 days before first dose of study treatment.
13. Patients receiving treatment with any enzyme-inducing anticonvulsant that cannot be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patients on non enzyme-inducing anticonvulsants are eligible.
14. Investigational agents within 4 weeks or ≤ 10 × half-life of the agent (whichever is longer) before first dose of study treatment.
15. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.

[redacted]

16. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective contraception during the study and for 3 months after stopping LDK378 treatment. Highly effective contraception is defined as any of:
    - Total abstinence: when this is in line with the preferred and usual lifestyle of the patient. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
    - Sterilization: have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    - Male partner sterilization (at least 6 months prior to screening) (With the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). (For female patients on the study the vasectomized male partner should be the sole partner for that patient).
    - Use of a **combination** of any two of the following (a+b or a+c or b+c):
        a. Use of oral, injected or implanted hormonal methods of contraception that have comparable efficacy (failure rate < 1%), for example hormonal vaginal ring or transdermal hormone contraception.
        b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
        c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

17. Sexually active males must use a condom during intercourse while taking the drug and for 3 months after stopping LDK378 treatment and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
18. Other severe, acute, or chronic medical conditions including uncontrolled diabetes mellitus or psychiatric conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results.
19. History of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).

[redacted]

6 Treatment

6.1 Study treatment

For this study, the term "investigational or study drug" refers to LDK378. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

LDK378 will be provided and supplied by Novartis. LDK378 is supplied as 150 mg hard gelatin capsules as individual open label patient supply. LDK378 will be dosed on a flat scale of 750 mg/day and not be adjusted to body weight or body surface area.

A complete cycle of treatment is defined as 28 days of once daily treatment of LDK378.

6.1.1 Dosing regimen

LDK378 will be administered orally once daily at a dose of 750 mg on a continuous dosing schedule in treatment period. The first 15 patients enrolled in the phase I component of the study will have PK sampling over 120-hour during the single-dose PK run-in period following a single oral dose at 750 mg. After the PK run-in period, the treatment period will start in which LDK378 will be given starting on Cycle 1 Day 1 in a continuous daily oral dosing regimen. The investigator must instruct the patient to take the study drug exactly as prescribed. Separately from these 15 patients, all the other enrolled patients will receive LDK378 treatment at 750 mg qd on Cycle 1 Day 1. The general dose and treatment schedule of the study treatments are listed in Table 6-1.

- All patients should take LDK378 daily at approximately the same time each day in the morning. On days that PK samples are obtained, the patient will take LDK378 during the clinic visit after the pre-dose PK samples and prior to post-dose PK samples, when instructed by the study staff.
- Patients should take LDK378 on an empty stomach (i.e. fast from food and drink, except water) at least 1 hour before or 2 hours after a light meal. Each dose of LDK378 should be taken with a glass of water and consumed over as short a time as possible (i.e. not slower than 1 capsule every 2 minutes).
- Patients should be instructed to swallow whole capsules and not to chew or open them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose.
- Patients should be instructed not to make up missed doses or partial doses (i.e. when the entire dose is not taken as instructed). A missed or partial dose will be defined as a case when the full dose is not taken within 8 hours after the approximate time of the usually daily dosing. That day's dose (or part remaining dose) should be omitted and the patient should continue treatment with the next scheduled dose on the following day.

[redacted]

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
LDK378	Gelatin capsule for oral use	750 mg (5 x 150 mg / capsule)	Once daily (28 day / cycle)

6.1.1.1 Additional dosing guidelines for pharmacokinetic sampling

On days with PK sampling the following additional guidelines should be followed:

- The patient should take the dose in the clinic at least two hours after a light breakfast. The patient does not have to fast overnight (See Section 7).
- The pre-dose sample should be drawn just before LDK378 dosing. The sampling time of the pre-dose PK sample and the dosing time of LDK378 must be precisely recorded in the eCRF. Furthermore, the dosing time of LDK378 on the previous day must be precisely recorded in the eCRF.
- If vomiting occurs within the first 6 hours post-treatment on a PK day, the exact time of the first vomiting episode must be noted.

6.1.2 Guidelines for continuation of treatment

For guidelines for dose modification of treatment, refer to Section 6.2.

Patients who have RECIST-defined PD by investigator assessment, but who, in the opinion of the investigator, have evidence of continued clinical benefit from LDK378 may continue to receive the study medication. In such cases, these patients must continue to be followed for safety assessments as per the schedule of assessments, but imaging assessments will no longer be required.

6.1.3 Treatment duration

Patients should continue LDK378, and should follow the protocol safety assessments as scheduled, until they experience any of the following:

- Disease progression (radiologically documented according to RECIST 1.1 by the investigator assessment) with the exception of patients, who, in the investigator's judgment, continue to show evidence of clinical benefit despite RECIST-defined PD (see Section 6.1.2)
- Unacceptable toxicity that precludes further treatment.
- Start of a new anti-cancer therapy.
- Pregnancy
- Treatment is discontinued at the discretion of the investigator or patient.
- Lost to follow-up
- Death
- Study terminated by Sponsor

[redacted]

Patients who permanently discontinue the study drug for any reason other than disease progression must, if consenting to further follow-up, continue efficacy follow-up assessments as scheduled in the protocol until the time of confirmed disease progression or death.

After discontinuing LDK378, further treatment for NSCLC is left to the physician's discretion.

6.1.4 Definition of treatment cycle

A treatment cycle is defined as 28 calendar days from the start of treatment with LDK378 (Day 1, cycle 1) for the purposes of scheduling procedures and evaluations.

6.2 Dose modifications

6.2.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Any changes in LDK378 administration must be recorded on the Dosage Administration Record eCRF.

General guidelines for dose modifications for toxicities other than those listed in Table 6-3.

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

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

More detailed LDK378 dose modification guidelines are described in Section 6.2.3. for selected toxicities. Any planned variance from these guidelines in view of patient safety must first be discussed with the sponsor unless there is an urgent need for action.

All dose modifications, interruptions or discontinuations must be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.03).

6.2.2 Treatment interruption and treatment discontinuation

If the administration of LDK378 is temporarily interrupted for reasons other than toxicity, then treatment with LDK378 may be resumed at the same dose. The same applies if the patient experiences an unacceptable toxicity not specifically described in Table 6-3 or Section 6.2.2, provided this toxicity resolved to ≤ CTCAE grade 1.

If the treatment with LDK378 is withheld due to toxicity, scheduled visits and all assessments should continue to be performed (with the exception of the dosing of the withheld study drug), as described in Table 7-1.

[redacted]

If the treatment with LDK378 dosing is withheld for more than 28 consecutive days (counting from the first day when a dose was missed), due to toxicity, then LDK378 should be permanently discontinued except in cases where the investigator believes the patient continues to derive clinical benefit. In such cases, treatment with LDK378 may be resumed at a lower dose.

Patients who discontinue the study due to a study drug related AE or an abnormal laboratory value must be followed as described in Section 6.2.4.

All patients will be followed for safety until 30 days after the last dose of LDK378. Patients whose treatment is temporarily interrupted or permanently discontinued due to an AE or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first, including all study assessments appropriate to monitor the event.

6.2.3 Criteria for LDK378 dose modifications

An LDK378 dose reduction will follow the guidelines described in Table 6-2. For each patient, a maximum of 3 dose modifications is allowed after which the patient must be discontinued from treatment with LDK378. Once the dose of LDK378 has been reduced, it cannot be re-escalated. If a patient continues treatment with LDK378 after RECIST-defined PD as determined by the investigator, the criteria for dose modification will also apply.

Table 6-2 Dose reduction steps for LDK378

LDK378 dose levels	Dose* and schedule
Starting dose level	750 qd continuously
Dose level – 1	600 qd continuously
Dose level – 2	450 qd continuously
Dose level – 3	300 qd continuously **

*Dose reduction should be based on the worst preceding toxicity
**Dose reduction below 300 mg/day is not allowed. If a dose reduction below 300 mg/day is required, the patient should be permanently discontinued from LDK378

Guidelines for dose modification and dose interruption of LDK378 are described in Table 6-3.

[redacted]

Table 6-3 Criteria for interruption and re-initiation of LDK378 treatment

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
HEMATOLOGICAL	
Neutropenia (ANC)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 and ≥ 1.0 x 10^9/L) Grade 3 (ANC < 1.0 and ≥ 0.5 x 10^9/L)	Maintain dose level
Grade 4 (ANC < 0.5 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Febrile neutropenia (ANC < 1.0 x 10^9/L, with a **single** temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)	Omit dose until clinically resolved and neutropenia ≤ Grade 2, then ↓ 1 dose level
Thrombocytopenia	
Grade 1 (PLT < LLN - 75 x 10^9/L) Grade 2 (PLT < 75 and ≥ 50 x 10^9/L)	Maintain dose level
Grade 3 (PLT < 50 and ≥ 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 4 (PLT < 25 x 10^9/L)	Omit dose until resolved to ≤ Grade 2, then ↓ 1 dose level
HEPATIC	
Alkaline phosphatase and/or Gamma-glutamyl transpeptidase (**GGT**)	
Isolated elevations of any grade	Maintain dose level
Total Bilirubin (for patients with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only)	
Grade 1 (> ULN and ≤ 1.5 x ULN)	Maintain dose level with liver function test (LFTs)*** monitored as per protocol
Grade 2 (> 1.5 and ≤ 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (> 3.0 and ≤ 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from LDK378

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from LDK378
AST or ALT	
Grade 1 (> ULN and ≤ 3.0 x ULN)	Maintain dose level with LFTs*** monitored per protocol
Grade 2 (> 3.0 and ≤ 5.0 x ULN) without total bilirubin elevation to > 2 x ULN	Maintain dose level with LFTs*** monitored per protocol
Grade 3 (> 5.0 and ≤ 20.0 x ULN) without total bilirubin elevation to > 2 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
AST or ALT and concurrent Total bilirubin	
AST or ALT > 3.0 x ULN with total bilirubin > 2.0 x ULN in the absence of cholestasis or hemolysis	Permanently discontinue patient from LDK378 Refer to Section 6.2.4.2 for additional follow-up
PANCREATIC	
Amylase and/or lipase elevations (in the absence of clinical symptoms)	
Grade 1 (> ULN and ≤1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 - 2.0 x ULN)	Maintain dose level
Grade ≥3 (> 2.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Note: Withhold ceritinib for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
RENAL	
Serum creatinine	
Grade 1 (>1 and ≤1.5 x baseline; > ULN and ≤1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 and ≤3.0 x baseline; >1.5 and ≤3.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level
Grade 3 (>3.0 x baseline; >3.0 and ≤6.0 x ULN)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (> 6.0 x ULN)	Permanently discontinue patient from LDK378

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
GASTROINTESTINAL	
Diarrhea**	
Grade 1	Maintain dose level but adjust anti-diarrhea treatment
Grade 2 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If diarrhea returns as ≥ Grade 2, then omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 3 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite maximal anti-diarrheal medication)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Nausea**	
Grade 1 or 2	Maintain dose level but adjust anti-emetic treatment
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Vomiting**	
Grade 1	Maintain dose level but adjust anti-emetic treatment
Grade 2 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then maintain dose level. If vomiting returns as ≥ Grade 2, then suspend dose until resolved to ≤ Grade 1, then ↓ 1 dose level.
Grade 3 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
Grade 4 (despite standard anti-emetics)	Omit dose until resolved to ≤ Grade 1, then ↓ 1 dose level
METABOLIC	
Any Grade **hypophosphatemia**	Treatment with phosphate supplements as clinically indicated and maintain dose level
Persistent **hyperglycemia** (glucose> 250 mg/dL) despite optimal anti-hyperglycemic therapy	Omit dose until hyperglycemia is adequately controlled, then resume LDK378 at ↓ 1 dose level If adequate hyperglycemic control cannot be achieved with optimal medical management, permanently discontinue patient from LDK378.
GENERAL DISORDERS	
Fatigue (asthenia)	
Grade 1 or 2	Maintain dose level
Grade 3	If grade 3 fatigue resolves to Grade 2 in ≤ 7 days, maintain dose level If grade 3 fatigue lasts > 7 days, omit dose until resolved to ≤ Grade 2 and then ↓ dose level

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
PULMONARY	
Notes: ● Withhold LDK378 for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD. ● During evaluation of potential grade 2, 3, and 4 pneumonitis, if an infectious etiology is confirmed (i.e., pneumonia) and pneumonitis is excluded, then consider resuming LDK378 at current dose level after the pneumonia resolves.	
PNEUMONITIS	
Any Grade treatment-related ILD/pneumonitis	Permanently discontinue patient from LDK378
CARDIAC	
Electrocardiogram QT corrected (QTc) interval prolonged	
Grade 1 (QTc 450-480 ms) Grade 2 (QTc 481-500 ms)	Maintain dose level
Grade 3 (QTc ≥ 501 ms on at least two separate ECGs)	Omit dose until QTc is less than 481 ms, then ↓ 1 dose level. - Assess the quality of the ECG recording and the QT value and repeat if needed. Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until QTc < 481 ms In addition: - Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia). If abnormal, correct abnormalities before resuming study drug treatment - Review concomitant medication use for drugs with the potential to increase the risk of drug exposure related to QT prolongation - Consider collecting a time-matched PK sample and record time and date of last study drug intake After resumption of dosing: -Repeat ECGs 7 days after dose resumption for all patients who had therapy interrupted due to QTc ≥ 501 ms.
Grade 4 (QTc ≥ 501 or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue patient from LDK378

[redacted]

Worst toxicity (CTCAE 4.03 Grade)*	**Dose Modifications for LDK378**
Bradycardia	
Grade 1 or 2	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm Evaluate concomitant medications known to cause bradycardia, and adjust the dose of LDK378.
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥ 60 bpm If the concomitant medication can be adjusted or discontinued, resume LDK378 at ↓ 1 dose level with frequent monitoring
Grade 4 (in patients who are not taking a concomitant medication also known to cause bradycardia or known to cause hypotension)	Permanently discontinue LDK378.
* Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All dose modifications should be based on the worst preceding toxicity. ** If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the Investigator. ***LFTs include albumin, ALT, AST, total bilirubin,alkaline phosphatase and GGT **** Dose modifications apply to patients who experience diarrhea despite appropriate antidiarrheal medication. This medication should be started at the first sign of abdominal cramping, loose stools or overt diarrhea (see Section 6.3.2.5) ***** Dose modifications apply to patients who experience nausea and/or vomiting despite appropriate antiemetic medication. This medication should be started at the first sign of nausea and/or vomiting (see Section 6.3.2.6)	

[redacted]

6.2.4 Follow-up for toxicities

An unscheduled visit should be performed in all cases below where toxicity monitoring is recommended more frequently than defined by the schedule of assessments (Table 7-1).

6.2.4.1 Guidelines for the follow-up of laboratory hematologic abnormalities

In case of any occurrence of febrile neutropenia, neutropenia ≥ grade 3 or thrombocytopenia ≥ grade 3, tests must be performed weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 2. Subsequent monitoring must be performed every 4 weeks. See Table 6-4.

6.2.4.2 Guidelines for the follow-up of laboratory liver abnormalities

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

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

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

Patients who discontinue study treatment due to liver toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks). Refer to Table 6-4.

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

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

- For patients with normal ALT and AST and TBIL value at baseline: AST or ALT > 3.0 x ULN combined with TBIL > 2.0 x ULN

[redacted]

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

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

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

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

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

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

6.2.4.3 Guidelines for the follow-up of laboratory renal abnormalities

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

In case of any occurrence of serum creatinine ≥ grade 3, tests must be performed twice weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1. Subsequent monitoring must be performed every 4 weeks. See Table 6-4.

[redacted]

6.2.4.4 Guidelines for monitoring pneumonitis

Monitor patients for pulmonary symptoms indicative of pneumonitis. In addition, withhold LDK378 for acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever and during diagnostic workup for pneumonitis/ILD.

See also dose modification guidelines described in Table 6-3.

6.2.4.5 Guidelines for the treatment of study drug induced nausea and vomiting

Nausea and vomiting are among the most frequently reported AES following treatment with LDK378 and patients must therefore be closely monitored for the appearance of these AEs.

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

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

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

Dose adaptation of LDK378 in case of treatment related nausea and/or vomiting must follow the guidelines presented above in Table 6-3.

6.2.4.6 Guidelines for the treatment of study drug induced diarrhea

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

The patient should be monitored for signs of dehydration and instructed to take preventive measures against dehydration as soon as diarrhea occurs. Antidiarrheal medication must be initiated at the first sign of abdominal cramping, loose stools or overt diarrhea. Concomitant medication for the treatment of diarrhea should follow local practice and the investigator's best judgment and may follow "the recommended guidelines for the treatment of cancer treatment-induced diarrhea" (Benson et al 2004). For example:

- For uncomplicated diarrhea (grade 1 or 2 without complicating signs or symptoms), loperamide given at a standard dose (e.g. initial administration of 4 mg, then 2 mg every 2-4 hours, maximum of 16 mg/day), along with oral hydration and dietetic measures should be considered. Note: complicating signs or symptoms include: moderate to severe cramping, decreased performance status, fever, neutropenia, frank bleeding or dehydration.

[redacted]

- For complicated diarrhea (all grade 3 or 4, grade 1-2 with complicating signs or symptoms), management should involve intravenous (IV) fluids, and consider treatment with octreotide (at starting dose of 100 to 150 µg SC tid or 25 to 50 µg IV) and antibiotics (e.g. fluoroquinolone) should be given.

Dose adaptation of LDK378 in case of treatment related diarrhea must follow the guidelines presented above in Table 6-3.

6.2.4.7 Guidelines for treatment of hypophosphatemia

In the phase I study [CLDK378X2101], there were 3 cases of grade 3 hypophosphatemia, one of which was a DLT that contributed to the MTD determination – this patient was able to continue LDK378 at the same dose. In all cases patients were able to continue therapy without dose modification. Hypophosphatemia was not among the commonly reported AEs (i.e., < 15%), regardless of relationship to LDK378 treatment. Therefore, phosphate levels will be checked at baseline and during treatment. In cases of hypophosphatemia at baseline, phosphate supplements should be started before treatment with LDK378. For any grade of hypophosphatemia during the study, treatment with phosphate supplements should be given as clinically indicated, and the LDK378 dose can be maintained.

6.2.4.8 Guidelines for the follow-up of laboratory pancreatic abnormalities

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

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

Patients who discontinue study treatment due to pancreatic toxicity must be monitored weekly (or more frequently if clinically indicated) until the event resolves to ≤ grade 1 or stabilization occurs (no CTCAE grade change over 4 weeks). Refer to Table 6-4.

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

See also dose modification guidelines described in Table 6-3.

[redacted]

Table 6-4 Follow-up evaluations for selected toxicities

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

*Note: this table refers to the evaluation schedule only. Refer to Table 6-3 for dose modifications required for applicable toxicities

6.2.5 Anticipated risks and safety concerns of the study treatment

Appropriate eligibility criteria and specific dose modification and stopping rules are included in this protocol. Recommended guidelines for prophylactic or supportive treatment for expected toxicities, including management of study-drug induced AEs, e.g., diarrhea are provided in Section 6.2.4. Refer to preclinical toxicity and or clinical data found in the [Investigator Brochure].

6.3 Concomitant medications

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g. such as anti-emetics, anti-diarrhea) is permitted (see Section 6.3.1), except when specifically prohibited (see Section 6.3.2).

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications including herbal/natural medications (excluding study treatment and prior antineoplastic treatments and blood transfusions), surgeries and procedures (including physical therapy) administered within 28 days prior to the first dose of administration of LDK378 through 30 days after the last dose of LDK378 will be recorded in the Concomitant Medications or Surgical and Medical Procedures eCRF, respectively. Medications include not only physician prescribed medications, but also all

[redacted]

over-the counter medications, herbal medications (prohibited, see Section 6.3.2.7), food and or vitamin supplements.

6.3.1 Permitted concomitant therapy

6.3.1.1 Corticosteroids

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

- Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular);
- Stable doses of corticosteroid therapy such as dexamethasone and prednisone (e.g. for tumor associated symptoms) are permitted during the course of the study. If increasing doses of corticosteroids are required, LDK378 must be withheld and the corticosteroid dose must have been stabilized (or decreasing) for at least 5 days before LDK378 is resumed.

6.3.1.2 Bisphosphonates

The use of bisphosphonates is allowed regardless of indication provided patients have been on stable doses optimally for at least 4 weeks prior to the start of treatment. Patients requiring initiation of bisphosphonate treatment during the course of the study should be evaluated for progressive disease unless disease progression is excluded and clearly documented in the patients' source documentation.

No drug-drug interaction is expected between LDK378 and bisphosphonates as the two drugs are eliminated through different elimination pathways. Bisphosphonates are not inhibitors of human CYP450 enzymes involved in the metabolism of LDK378 and do not undergo metabolism *in vivo*.

The same guidelines apply to the use of denosumab for the treatment of bone metastatic disease.

6.3.1.3 Drugs that are metabolized by CYP450 enzymes

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

Concomitant treatment of LDK378 with weak inhibitors or inducers of CYP3A4/5 is permitted. Caution is advised when LDK378 is co-administered with drugs that are moderate inhibitors or inducers of CYP3A4/5 (Table 14-2 of Appendix 1). Duration of concomitant

[redacted]

treatment should be kept as short as possible (e.g. less than 1 week), or completely avoided whenever possible. Patients receiving such medications must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require dose titration or adjustment. Note that co-administration of LDK378 with strong inhibitors or inducers of CYP3A4/5 is prohibited (refer to Section 6.3.2.5).

Concomitant treatment of LDK378 with medications known to be metabolized by CYP2C9, and CYP3A4 is allowed with caution (Table 14-2 of Appendix 1), except for drugs which have narrow therapeutic index/sensitive substrates for these CYP isoforms (Table 14-1 of Appendix 1).

6.3.1.4 Non-enzyme inducing anti-epileptic drugs

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

6.3.1.5 Palliative radiotherapy and surgery

Local radiotherapy for analgesic purposes or for lytic lesions at risk of fracture may be carried out if required. If palliative radiotherapy is initiated after start of study treatment, the reason for its use must be clearly documented and progression as per RECIST 1.1 must be assessed and documented.

Patients who develop progressive disease but are still deriving clinical benefit from ceritinib therapy, as determined by the Investigator may undergo radiotherapy and/or surgical resection as palliative localized therapy to treat metastatic lesions. Ceritinib should be held for at least 4 days prior to radiotherapy and at least 1 day prior to any surgery. Ceritinib may be resumed ≥3 days after completing radiotherapy or minor surgery, and ≥2 weeks after major surgery.

6.3.1.6 Gastric protection agents

The use of gastric protection agents except for proton pump inhibitors (PPIs) is allowed (see Section 6.3.2.7). When the concurrent use of a H2-antagonists or an antacid is necessary, the H2 blocker may be administered 10 hours before and 2 hours after LDK378 dose, or the antacid be administered 2 hours before or 2 hours after LDK378 dose. Time restrictions for the concurrent use of PPIs and LDK378 are not applicable due to the long-acting effects of PPIs on gastric pH (i.e., separation of doses will not likely impact this interaction).

6.3.2 Prohibited concomitant therapy

6.3.2.1 Other anticancer therapy

Anticancer therapy (chemotherapy, targeted therapy, biologic therapy or radiation therapy (except palliative radiotherapy as described in Section 6.3.1.5), and anti-cancer surgery) other than the study treatment must not be given to patients while they are enrolled in the treatment portion of the trial. If such agents are required then the patient must be permanently discontinued from the treatment portion of the study.

[redacted]

6.3.2.2 Other investigational therapies

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

6.3.2.3 Warfarin and coumarin derivatives

Therapeutic doses of warfarin sodium or any other coumarin-derivative anticoagulant are not permitted. LDK378 is an inhibitor of and CYP2C9, the major metabolizing enzyme of warfarin. A clinically relevant increase in warfarin exposure is possible.

6.3.2.4 Enzyme inducing anti-epileptic drug

Use of EIAEDs is not permitted. Refer to Table 14-3 of Appendix 1 for a list of prohibited EIAED.

If a patient is currently taking an EIAED, he/she must have discontinued the EIAED therapy for at least 1 week prior to starting study drug.

If a patient was previously on a non-EIAED and needs to permanently change anticonvulsant agent but cannot change to another non-EIAED, the patient will be taken off LDK378.

6.3.2.5 Strong CYP3A inhibitors and inducers

In vitro metabolism studies suggest that oxidative metabolism of LDK378 is predominantly mediated by CYP3A4/5.

Strong inhibitors or inducers of CYP3A4/5 are prohibited. Patients receiving concomitant medications known to strongly inhibit and/or induce CYP3A4/5 that are deemed medically necessary should be excluded from the study. Refer to Table 14-1 of Appendix 1 for a list of these medications. Please note that this list may not be comprehensive.

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

LDK378 is a potent inhibitor of drugs metabolized by the cytochromes CYP2C9 and CYP3A4/5 *in vitro*. Because of the potential risk for drug-drug interactions, using medications known to be metabolized by these enzymes and that have a narrow therapeutic index is not permitted concomitantly with LDK378. Refer to Table 14-1 of Appendix 1 for a list of these medications. Please note that this list may not be comprehensive.

6.3.2.7 Gastric protection agents

The use of gastric protection agents including antacids, H2-antagonists, and proton pump inhibitors (PPIs; Table 14-2 of Appendix 1) is allowed. However, PPIs should be used with caution due to the theoretical effects of long-acting pH elevating agents (i.e., prolonged acid suppression) on reducing LDK378 absorption. When the concurrent use of a H2-antagonist or an antacid with LDK378 is necessary, the H2 blocker must be administered 10 hours before or 2 hours after the LDK378 dose, and the antacid must be administered 2 hours before or 2 hours after the LDK378 dose. Time restrictions for the concurrent use of PPIs and LDK378 are not applicable due to the long-acting effects of PPIs on gastric pH (i.e., separation of doses will not likely impact this interaction).

[redacted]

6.3.2.8 Herbal medications

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

Patients should stop using herbal medications at least 7 days prior to first dose of study treatment.

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

LDK378 has potent activity on the hERG channel with an IC_{50} of 0.4 μM. However, there were no LDK378-related effects *in vivo* in monkeys at doses as high as 100 mg/kg (human equivalent dose [HED] of 1950 mg). Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of LDK378 on the QT interval in an open-label, dose-escalation, and expansion study ([CLDK378X2101]). A total of 304 patients were treated with LDK 378 doses ranging from 50 to 750 mg with 255 patients treated with LDK378 750 mg. One of 304 patients (<1%) was found to have a QTc >500 msec and 10 patients (3.3%) had an increase from baseline QTc >60 msec. At average steady-state concentrations the upper bound of the 2-sided 90% CI for QTc change from baseline was 16 msec at LDK 378 750 mg. A pharmacokinetic/pharmacodynamic analysis suggested concentration-dependent QTc interval prolongation.

Concomitant administration of LDK378 with drugs known to have a high risk of increasing the QTc interval, and drugs known to increase the QTc interval that are also primarily metabolized by CYP3A4/5 should be avoided. Concomitant use of LDK378 and any medication included in Table 14-1 of Appendix 1 titled "List of prohibited QT prolonging drugs" (i.e., drugs that are generally accepted by the Qtdrugs.org Advisory Board of the Arizona CERT to have a known risk of causing Torsades de Pointes) is not permitted.

6.4 Patient numbering, treatment assignment or randomization

6.4.1 Patient numbering

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

At the screening visit, the investigator or designated staff will contact the Interactive Response Technology (IRT) system and provide the requested identifying information for the patient to register them into the IRT system. Once assigned, the Subject No. must not be reused for any other subject and the Subject No. for that individual must not be changed, even

[redacted]

if the patient is re-screened. If the patient fails to start treatment for any reason, the reason will be entered into the Screening Disposition eCRF page.

Following completion of screening procedures The IRT system must again be contacted to verify patient eligibility and enroll the patient in the study before the patient receives the first dose (at PK-run in Day 1 for the first 15 patients and at C1D1 for all other patients). If the patient is a screen failure, IRT should be notified within 2 working days that the patient was a screen failure and was not enrolled.

6.4.2 Treatment assignment or randomization

Not applicable.

6.4.3 Treatment blinding

Not applicable.

6.5 Study drug preparation and dispensation

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

The site pharmacy will receive open label medication containing LDK378 capsules. Medication will be dispensed based on the appropriate dose with instructions from the investigator on how to take the medication.

Table 6-5 Preparation and dispensing

Study treatments	Dispensing	Preparation
LDK378	Capsules including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study treatment for self-administration at home until at least their next scheduled study visit.	Not applicable

6.5.1 Study drug packaging and labeling

The study medication packaging has a 2-part label. Immediately before dispensing the package to the patient, site personnel will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

[redacted]

Table 6-6 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
LDK378	150 mg capsules	LDK378 (daily)

6.5.2 Drug supply and storage

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

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

Compliance will be assured by administrations of the study treatment under the supervision of investigator or his/her designee, and will be verified by determinations of LDK378 in plasma and/or urine.

6.5.3.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Drug accountability will be noted by the field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

At study close-out, and, as appropriate during the course of the study, the investigator will return all used and unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.5.3.3 Handling of other study treatment

Not applicable.

6.5.4 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility or third party, as appropriate, or locally at the site only if permitted by local regulations and authorized by Novartis.

[redacted]

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments and indicates with an "X" the visits when they are performed. Each treatment cycle is 28 days (the 28 days cycle length is fixed regardless of whether the dose of LDK378 is withheld). All visits are to be scheduled according to the appropriate number of calendar days from Cycle 1 Day 1 of study drug administration. A visit window of +/- 1 day in Cycle 1 and +/- 3 days in Cycle 2 onwards is allowed. Imaging evaluations may be performed +/-7 days of the due date of the assessment. **Note: If treatment with LDK378 is withheld at any time during the study, all study visits, safety and efficacy assessments should continue according to the appropriate number of calendar days from Cycle 1 Day 1 as per the schedule of assessments.**

All data obtained from these assessments must be supported in the patients' source documentation. No eCRF will be used as a source document. The table indicates which assessments produce data to be entered into the database (D) or remain in the source documents only (S).

[redacted]

Table 7-1 Visit evaluation schedule

	Category	Protocol section TBC	Screening Phase	PK Run-In Phase [a,b]		Treatment Phase					Post-treatment efficacy follow-up if no PD at the EOT		Survival follow-up
						Cycles 1 (28 d)			Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Screening Visit (Day -28 to Day -1)**	**Run-In Day 1**	**Run-In Days 2, 3, 4 and 5**	**Cycle 1, Day 1**	**Cycle 1, Day 8**	**Cycle 1, Day 15**	**Cycle 2, Day 1; Cycle 3, Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**End of post-treatment study phase**	**Survival follow-up**
Obtain Main Informed Consent	D	7.1.2	X										
[redacted]													
Collection of documentation of ALK rearrangement OR confirmation of ALK status by central laboratory	D	7.1.1 7.1.2	New biopsy preferred and/or archival tissue & pathology report										
ALK test performed on archival specimen	D	7.1.1.1	X										
ALK test performed on new tumor biopsy	D	7.1.1.1	X										

[redacted]

	Category	Protocol section TBC	Screening Phase	PK Run-In Phase [a,b]		Treatment Phase					Post-treatment efficacy follow-up if no PD at the EOT		Survival follow-up
						Cycles 1 (28 d)			Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Screening Visit (Day -28 to Day -1)**	**Run-In Day 1**	**Run-In Days 2, 3, 4 and 5**	**Cycle 1, Day 1**	**Cycle 1, Day 8**	**Cycle 1, Day 15**	**Cycle 2, Day 1; Cycle 3, Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**End of post-treatment study phase**	**Survival follow-up**
[redacted]													
End of Phase Disposition Page	D	7.1	X							X		X	
Demography	D	7.1.2.3	X										
Inclusion/ exclusion criteria	D	5.2 5.3	X										
Eligibility check	D	6.4.1	X										
Relevant medical history/ current medical conditions	D	7.1.2.3	X										
History or smoking	D	7.1.2.3	X										
Diagnosis and extent of cancer	D	7.1.2.3	X										

[redacted]

	Category	Protocol section TBC	Screening Phase	PK Run-In Phase [a,b]		Treatment Phase					Post-treatment efficacy follow-up if no PD at the EOT		Survival follow-up
						Cycles 1 (28 d)			Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Screening Visit (Day -28 to Day -1)**	**Run-In Day 1**	**Run-In Days 2, 3, 4 and 5**	**Cycle 1, Day 1**	**Cycle 1, Day 8**	**Cycle 1, Day 15**	**Cycle 2, Day 1; Cycle 3, Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**End of post-treatment study phase**	**Survival follow-up**
Prior antineoplastic therapies (meds, surgery, radiation)	D	7.1.2.3	X										
Prior and concomitant medications	D	7.1.2.3	Continuous										
Physical examination	S	7.2.2.1	X	X		X	X	X	X	X			
Performance status	D	7.2.2.4	X	X		X			X	X			
Height	D	7.2.2.3	X										
Weight	D	7.2.2.3	X	X		X			X	X			
Vital signs	D	7.2.2.2	X	X	X	X	X	X	X	X			
Laboratory assessments		7.2.2.5											
Hematology	D	7.2.2.5.1	X	X		X	X	X	X	X			
Blood chemistry	D	7.2.2.5.2	X	X		X	X	X	X	X			
Urinalysis (dipstick) with micro-analysis	D	7.2.2.5.3	X	X									

[redacted]

	Category	Protocol section TBC	Screening Phase	PK Run-In Phase [a,b]		Treatment Phase					Post-treatment efficacy follow-up if no PD at the EOT		Survival follow-up
						Cycles 1 (28 d)			Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Screening Visit (Day -28 to Day -1)**	**Run-In Day 1**	**Run-In Days 2, 3, 4 and 5**	**Cycle 1, Day 1**	**Cycle 1, Day 8**	**Cycle 1, Day 15**	**Cycle 2, Day 1; Cycle 3, Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**End of post-treatment study phase**	**Survival follow-up**
Serum pregnancy test	D	7.2.2.5.4	X										
Urine pregnancy test (prior to dosing)		7.2.2.5.4		X		X			X	X			
Testosterone (total and free), LH, FSH, steroid hormone binding globulin (SHBG) (males only)	D	7.2.2.5.5	X	X		X	X	X					
Coagulation	D	7.2.2.5.6	X										
Imaging Tumor Evaluations		7.2.1											
CT scan or MRI of chest and abdomen	D	7.2.1	X						Cycles 3 then every 2nd cycle (i.e. every 8 weeks)	X	Every 8 weeks following EOT until PD		
Whole body bone scan	D	7.2.1	X										

[redacted]

	Category	Protocol section TBC	Screening Phase	PK Run-In Phase [a,b]		Treatment Phase					Post-treatment efficacy follow-up if no PD at the EOT		Survival follow-up
						Cycles 1 (28 d)			Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Screening Visit (Day -28 to Day -1)**	**Run-In Day 1**	**Run-In Days 2, 3, 4 and 5**	**Cycle 1, Day 1**	**Cycle 1, Day 8**	**Cycle 1, Day 15**	**Cycle 2, Day 1; Cycle 3, Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**End of post-treatment study phase**	**Survival follow-up**
CT scan or MRI of other metastatic sites (e.g. neck, pelvis, etc) Localized bone CT scan, MRI or x-ray (for any lesions identified on the whole body bone scan that are not visible on the chest/abdomen CT scan or MRI) Photography (for any skin lesions)	D	7.2.1	X (if clinically indicated)						Cycles 3 then every 2nd cycle (i.e. every 8 weeks): only if positive at baseline or clinically indicated	Only if positive at baseline or clinically indicated	Every 8 weeks following EOT until PD (only if positive at baseline or clinically indicated)		

[redacted]

	Category	Protocol section TBC	Screening Phase	PK Run-In Phase [a,b]		Treatment Phase					Post-treatment efficacy follow-up if no PD at the EOT		Survival follow-up
						Cycles 1 (28 d)			Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Screening Visit (Day -28 to Day -1)**	**Run-In Day 1**	**Run-In Days 2, 3, 4 and 5**	**Cycle 1, Day 1**	**Cycle 1, Day 8**	**Cycle 1, Day 15**	**Cycle 2, Day 1; Cycle 3, Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**End of post-treatment study phase**	**Survival follow-up**
CT scan or MRI of brain	D	7.2.1	X						Cycles 3 then every 2nd cycle (i.e. every 8 weeks): only if clinically indicated or positive at baseline	Only if clinically indicated or positive at baseline	Every 8 weeks following EOT until PD (only if clinically indicated or positive at baseline)		
Study drug administration		6.1.1											
LDK378 dosing	D	6.1.1		X		Continuous							
Safety		8.1											
Adverse events	D	8.1	Continuous										
ECG	D	7.2.2.6.1 Table 7-4 Table 7-5	X	See Table 7-4 and Table 7-5 for ECG schedule									
[redacted]													

[redacted]

	Category	Protocol section TBC	Screening Phase	PK Run-In Phase [a,b]		Treatment Phase					Post-treatment efficacy follow-up if no PD at the EOT		Survival follow-up
						Cycles 1 (28 d)			Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Screening Visit (Day -28 to Day -1)**	**Run-In Day 1**	**Run-In Days 2, 3, 4 and 5**	**Cycle 1, Day 1**	**Cycle 1, Day 8**	**Cycle 1, Day 15**	**Cycle 2, Day 1; Cycle 3, Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**End of post-treatment study phase**	**Survival follow-up**
[redacted]													
PK sampling	D	7.2.3 Table 7-6 Table 7-7		See Table 7-6 and Table 7-7 for PK schedule									
Meal record	D	7.2.3		X		X	X		X Cycle 2 Day 1 only				
Survival follow-up		7.1.7.3											

[redacted]

	Category	Protocol section TBC	Screening Phase	PK Run-In Phase [a,b]		Treatment Phase					Post-treatment efficacy follow-up if no PD at the EOT		Survival follow-up
						Cycles 1 (28 d)			Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			Screening Visit (Day -28 to Day -1)	Run-In Day 1	Run-In Days 2, 3, 4 and 5	Cycle 1, Day 1	Cycle 1, Day 8	Cycle 1, Day 15	Cycle 2, Day 1; Cycle 3, Day 1; etc.	End of treatment visit	Tumor follow-up	End of post-treatment study phase	Survival follow-up
Antineoplastic therapies since discontinuation of study treatment	D	7.1.7.3									X		X
Survival assessment	D	7.1.7.3											X

[redacted]

7.1.1 Molecular screening

Histologically or cytologically confirmed diagnosis of locally advanced or metastatic NSCLC that carries an ALK rearrangement, defined as positive using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria) or positive as assessed by the CFDA approved immunohistochemistry (IHC) test (Ventana Medical Systems, Inc) using rabbit monoclonal primary antibody assay (D5F3) and associated scoring algorithm. If documentation of ALK rearrangement is not available as described above, a test to confirm ALK rearrangement must be performed using an archival tumor obtained at or since the time of diagnosis or a new tumor biopsy obtained prior to the first LDK378 dose. The test will be performed at a Novartis designated central laboratory (by IHC test using rabbit monoclonal primary antibody assay (D5F3), Ventana Medical Systems, Inc). Patients must wait for the result of the ALK rearrangement status before initiating treatment with LDK378.

7.1.1.1 Tumor sample requirements for central laboratory analysis

The Informed Consent Form (ICF) will allow for a tumor sample to be collected and shipped to a Novartis-designated central laboratory for analysis. Archival tumor tissue (block or slides) and/or a fresh tumor biopsy will be tested for ALK rearrangement and will be used to determine study eligibility for patients that do not have available documentation of ALK rearrangement at Screening. Acceptable archival tumor tissue may consist of a formalin fixed paraffin embedded (FFPE) block tumor tissue or at least 7, preferably 15, slides 4-5 μm thick. Archival specimens must be submitted with a copy of the corresponding pathology report. Results of the assay will be sent to the site. If delays are experienced in processing the sample, the screening site will be informed.

If a tumor tissue block is provided, the remaining tissue will be returned to the site upon request.

If both archival and fresh tumor tissue is made available for analysis, ALK status testing will be conducted using the fresh specimen and the archival tumor tissue will be used for exploratory studies. If biopsies from multiple tumor sites are available, the primary (vs. metastatic) tumor is the preferred sample for ALK status testing.

[redacted]

7.1.2 Screening

Written informed consent must be obtained before any study specific procedure is performed. Screening assessments to confirm eligibility into the main study should be performed as per the schedule of assessments. Patients that do not have available documentation of ALK rearrangement at Screening must wait for result of the ALK rearrangement status before initiating treatment with LDK378.

[redacted]

Re-screening of patients will not be allowed, but laboratory parameters which do not meet the inclusion criteria may be re-tested within the screening window (Day -28 to Day -1). Laboratory assessments performed as part of the screening evaluations will not be required to be repeated prior to dosing (except urine pregnancy test). The cardiac eligibility criteria should be assessed with the central ECG report. Tumor imaging assessments will be performed at screening between Day -28 and Day -1. Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF can be considered as the baseline images for this study.

7.1.2.1 Eligibility screening

Following registering in the IRT for screening, patient eligibility will be checked once all screening procedures are completed. The eligibility check will be embedded in the IRT system. Please refer to and comply with the detailed guidelines in the IRT manual.

7.1.2.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screening failure.

The following eCRFs must be completed for screening failure patients:

- Screening Phase Disposition page (including reason for not being started on treatment)
- Informed consent
- Demography
- Adverse Events (only if an SAE occurs)
- Inclusion/Exclusion criteria

7.1.2.3 Patient demographics and other baseline characteristics

Data to be collected on patient characteristics at screening include:

- Demography (including: date of birth, age, patient initials, gender, childbearing potential, race and ethnicity, or as allowed by local regulations)
- Relevant medical history
- History of smoking
- NSCLC diagnosis and extent of disease, including:
  - Date of diagnosis of NSCLC
  - ALK status documentation
  - Site of active disease
  - Characteristics of disease
- Prior antineoplastic therapies (medications, radiation, surgeries)

[redacted]

- Prior and Concomitant Medications, surgical and medical procedures

All other medications taken within 28 days before the first dose of study treatment is administered must be recorded on the Prior and Concomitant medication eCRF page and updated on a continual basis if there is new change to the medication.

7.1.3 PK Run-in period

The first 15 patients enrolled will participate in a single-dose PK run-in period. Additional patients may be enrolled in the study with PK run-in period in case PK profiles from some of the enrolled patients are deemed not evaluable due to early discontinuation from the study or due to vomiting events on the day of PK sampling. In order to characterize the pharmacokinetics of LDK378 in Chinese patients, a single-dose PK run-in period of 5 days will be completed. Since the Cycle 1 Day 1 pre-dose PK collection is considered the 120 hours post-dose PK time point of the PK run-in period, if possible, Cycle 1 Day 1 should immediately follow the 5-day PK run-in phase. If a break between Day 5 of the PK run-in period and Day 1 of Cycle 1 occurs, a 120 hour post-dose PK sample should be collected on the 6th day of the PK run-in phase and no pre-dose PK sample should be collected at Cycle 1 Day 1.

For details of assessments during the PK run-in period, refer to Table 7-4.

7.1.4 Treatment period

The study treatment phase begins on Cycle 1, Day 1 with the first administration of LDK378 and will continue until unacceptable toxicity that precludes further treatment, start of a new anti-cancer therapy, treatment is discontinued at the discretion of the investigator and/or patient death. If a patient experiences disease progression (radiologically documented according to RECIST 1.1 by investigator assessment), LDK378 administration may be stopped, or may be continued if the patient is continuing to derive clinical benefit in the opinion of the investigator.

Patients will be assessed as per visit schedule in Table 7-1.

Visit windows of ± 1 calendar day will be applicable to scheduled study assessments during Cycle 1. Visit windows of ± 3 days from scheduled study assessments will apply during and beyond Cycle 2. The only exception is imaging assessments, which have a ± 7 day window at all scheduled time points.

7.1.5 Discontinuation of study treatment

A patient will be defined as on the study if they are continuing to have any study data collected, i.e. if the patient is being treated with LDK378, is in efficacy follow-up after discontinuing LDK378, or is in survival follow-up.

Patients may voluntarily withdraw from study treatment for any reason at any time. In this situation, the patient should be encouraged to consent to be followed for tumor assessments until the development of Progressive Disease (as assessed by investigator) and/or survival. If a patient decides to discontinue from the study treatment, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and

[redacted]

record this information in the patient's chart and on the appropriate CRF pages. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

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

Patients must permanently stop the study treatment if one of the following occurs:

- Pregnancy
- Study Terminated by Sponsor
- Patient/guardian decision
- Physician decision
- Lost to follow-up
- Death

Patients may permanently stop the study treatment for one of the following reasons:

- Progression of disease (radiological as assessed by investigator)
- AEs
- Non-compliance with study treatment
- Technical Problems
- Use of prohibited treatment
- - Any protocol deviation that results in a significant risk to the patient's safety

Patients who become pregnant during the trial must be withdrawn (Section 8.4). Patients who become pregnant must cease all tumor assessments regardless of whether or not they developed Progressive Disease.

Patients who discontinue study treatment during the treatment phase should NOT be considered withdrawn from the study. They should be scheduled for a visit as soon as possible and within 7 days after the last dose of study treatment, at which time all of the assessments listed for the EOT visit will be performed. If a patient withdraws from treatment at a study visit, EOT assessments do not need to be repeated. An End of Treatment Phase Disposition eCRF page should be completed, giving the date and reason for stopping LDK378 treatment.

Patients who have RECIST-defined PD by investigator assessment, but who, in the opinion of the investigator, have evidence of continued clinical benefit from LDK378 may continue to receive this drug. These patients will continue assessments as detailed in Table 7-1 except tumor and [redacted]. In such cases, patients must complete the EOT visit only after permanent discontinuation of LDK378. An End of Treatment Phase Disposition eCRF page should be completed, giving the date and reason for stopping the study treatment.

At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study treatment.

If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the survival status.

[redacted]

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If a patient discontinues study treatment, but continues study assessments, (e.g. during post treatment follow up phase as detailed in Table 7-1), the patient remains on study until such time as he/she completes protocol criteria for ending study assessments. At that time, the reason for study completion should be recorded on the End of Post Treatment (Study Phase Completion) Disposition eCRF page.

If using IRT, the Investigator must contact the IRT to register the subject's discontinuation from treatment.

Patients who discontinue study treatment should enter the survival follow-up period or continue tumor assessments when appropriate. Tumor assessments will continue until the investigator assessment determined disease progression, patient withdraws consent from tumor assessments patient is lost to follow-up, death or study terminated by Sponsor.

If a patient will have no further study data collected because he/she withdraws from the study completely, the investigator must determine the primary reason for a patient's premature withdrawal from the study and record this information on the Study Phase Completion Disposition eCRF as applicable. The investigator must show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If the patient was still taking study medication at the time of the withdrawal, the End of Treatment eCRF should also be completed.

Patients may voluntarily withdraw from the study or be discontinued from the study at the discretion of the investigator at any time.

7.1.5.1 Replacement policy

Patients lost to follow-up or withdrawing consent from the study without observed PFS events will be censored for the primary analysis and will not be replaced.

7.1.6 Withdrawal of Consent

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

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

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

[redacted]

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

7.1.7 Follow up period

7.1.7.1 Safety follow up

All patients will be followed for AEs and SAEs for at least 30 days following the last dose of study treatment at the end of treatment phase.

At the end of this period, the investigator should assess and discuss with the patient any AE observed/concomitant medication taken since discontinuation of study treatment.

Patients whose treatment is permanently discontinued due to an AE (clinical or based on abnormal laboratory value) must be followed until resolution or stabilization of the event, whichever comes first. In case of an abnormal laboratory value, blood tests should be repeated until resolution or stabilization.

7.1.7.2 Post-Treatment Follow-up

All patients who discontinued treatment during the treatment phase for reasons other than death, lost to follow-up, pregnancy or disease progression as per investigator assessment (Section 7.1.3) will continue tumor and [redacted] as per Table 7-1 (every 8 weeks) thereafter until PD as per investigator assessment, withdrawal of consent or death. Once the patient ceases tumor follow-up, the reason for completion should be recorded on the End of Post Treatment Disposition (Study Phase Completion) eCRF page.

7.1.7.3 Survival follow-up

All patients who progressed (PD) as per investigator assessment, have started a new anti-neoplastic therapy, and/or withdrew consent from further study assessments will subsequently be followed for survival information every 12 weeks until death, lost to follow-up or withdrawal of consent for survival. The investigator or his designee will collect this survival information and any new anti-neoplastic therapies for all patients until the final survival analysis.

Follow-up can be done via a phone contact. Antineoplastic therapies will be captured on the 'Antineoplastic therapies since discontinuation of study treatment' eCRF page following the last dose of the study treatment.

7.1.7.4 Lost to follow-up

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

[redacted]

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor evaluation will be determined locally by investigator assessment according to the Novartis guideline (Version 3.1, Appendix 2) on the Response Evaluation Criteria in Solid Tumors (RECIST), based on RECIST Version 1.1 (Eisenhauer et al 2009). The investigator assessment will be used for the primary endpoint analysis. Additionally, imaging data will be centrally collected, checked for quality and independently reviewed by an imaging vendor designated by Novartis and will be the basis of supportive analyses.

7.2.1.1 Baseline assessments

Tumor evaluation will be performed at baseline within 28 days of, and prior to study treatment.

Contrast-enhanced CT (or MRI) should preferably be performed using a 5 mm slice thickness with a contiguous reconstruction algorithm. CT/MRI scan slice thickness should not exceed 8 mm cuts using a contiguous reconstruction algorithm.

Required conditions for tumor assessment at baseline

- Patients must have measurable disease as per RECIST v1.1 (Appendix 2). Measurable lesions include lytic or mixed (lytic + blastic) bone lesions with an identifiable soft tissue component that meets the measurability criteria per RECIST v1.1 (Appendix 2).
- Patients with only non-measurable lesions are not eligible.
- If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- Any potentially measurable lesion that has been previously treated with radiotherapy should be considered as a non-measurable lesion. However, if a lesion previously treated with radiotherapy has clearly progressed since the radiotherapy, it can be considered as a measurable lesion.
- All measurable lesions up to a maximum of 5 nodal and/or non-nodal lesions in total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.

Required image assessments for tumor assessment at baseline

The following assessments will be performed:

- Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of chest and abdomen.
    - The preferred radiologic technique is CT with intravenous (i.v.) contrast. If a patient is known to have a contraindication to CT contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts) plus a contrast-enhanced MRI (if possible) of the abdomen should be performed.

[redacted]

- A whole body bone scan according to institutional guidelines (e.g. Tc-99 bone scan, whole body bone MRI, FDG-PET or sodium fluoride positron emission tomography (NaF PET)).
- Localized CT, MRI or X-rays of all skeletal lesions identified on the screening bone scan, which are not visible on the chest and abdomen CT/MRI (and pelvis CT/MRI if applicable)
- Brain CT or MRI scan should be completed in order to assess CNS disease. Contrast enhanced brain MRI is preferred, however, if MRI contrast is contraindicated, then brain MRI without contrast or brain CT with/without contrast is acceptable.
- Color photographs (with a metric ruler) if skin lesions are present.
- CT or MRI of any other site of disease not captured by any of the above listed images (e.g., pelvis, neck) as clinically indicated.

Any imaging assessments already completed during the regular work-up of the patient within 28 days prior to start of treatment, including before signing the main study ICF can be considered as the baseline images for this study. After screening, scans need not be repeated, unless clinically indicated. If indicated, the same methodology as at screening should be used.

Chest x-ray or ultrasound should not be used to measure tumor lesions.

7.2.1.2 Subsequent image assessments for response determination

Tumor assessment for response determination will be made every 8 weeks starting from Day 1 of cycle 1 (+/- 7 days window). The 8 weeks interval should be respected regardless of whether treatment with LDK378 is temporarily withheld.

Post-baseline tumor assessments

The following assessments will be performed at on-study scheduled visits (see Table 7-1):

- Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of chest and abdomen.
- Localized CT, MRI or X-rays of all skeletal lesions identified on the screening bone scan, which are not visible on the chest and abdomen CT/MRI (and pelvis CT/MRI if applicable). Whole body bone scans need not be repeated after baseline unless clinically indicated.
- Brain CT or MRI, if brain metastases were identified at baseline.
- Color photographs (with a metric ruler) if skin lesions were documented at baseline.
- CT or MRI of any other site of disease documented at baseline (e.g., pelvis, neck).

For post-baseline tumor assessments, all lesions that were present at baseline must be accounted for using the same technique as used at baseline so that the comparison is consistent. If possible, a single radiologist should perform all tumor response evaluations for an individual patient.

All study imaging performed, including any intercurrent imaging studies, whether or not suspected to fulfill a progression or response criterion, should be submitted to the designated imaging CRO for quality control promptly after acquisition.

[redacted]

Criteria required for determining partial or complete response should be confirmed by a subsequent imaging assessment at least 4 weeks later. If an off-schedule imaging assessment is performed to confirm response or if progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule unless the next scheduled imaging timepoint is within 2 weeks, in which case the scheduled imaging timepoint can be omitted.

Combined PET/CT may be used only if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of oral and IV contrast media. At the discretion of the Investigators, FDG-PET scans may be performed to document progressive disease per RECIST 1.1 (Appendix 2).

Duration of post-baseline tumor assessments

Tumor assessments will be done until RECIST-defined PD by investigator assessment, death, lost to follow-up, or patient decision involving withdrawal of consent.

If a patient discontinues study treatment in the absence of PD, tumor assessments will continue to be done every 8 weeks until RECIST-defined PD by investigator assessment, death, lost to follow-up, or patient decision involving withdrawal of consent.

If a patient continues treatment with LDK378 after RECIST-defined PD by investigator assessment, no further imaging assessments on study are required.

Imaging evaluations will also be performed at the End of Treatment (EOT) visit. If a patient is known to have PD at a scheduled study visit, EOT imaging evaluations do not need to be repeated for the EOT visit.

7.2.2 Safety and tolerability assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every visit. For details on AE collection and reporting, refer to Section 8. Significant findings that were present prior to the signing of informed consent must be included in the relevant medical history/current medical conditions page on the patient's eCRF. Significant new findings that begin or worsen after informed consent must be recorded on the Adverse Event page of the patient's eCRF.

7.2.2.1 Physical examination

Physical examinations will include an examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and a basic nervous system evaluation. Information about the physical examination must be present in the source documentation at the study center. For the assessment schedule refer to Table 7-1.

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

[redacted]

7.2.2.2 Vital signs

Vital signs include body temperature, blood pressure and pulse measurements. Blood pressure (systolic and diastolic) and pulse should be measured after the patient has been sitting for five minutes. For patients participating in the extensive ECG subset, see Section 7.2.2.6.1 and Table 7-6.

For the assessment schedule refer to Table 7-1.

7.2.2.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured. Height will be measured at screening only. For the assessment schedule for weight refer to Table 7-1.

7.2.2.4 Performance status

WHO performance status will be assessed as per the assessment schedule (refer to Table 7-1). Assessment of WHO performance status (Table 7-2) will be performed within the time windows described above of the scheduled assessment, even if study treatment is being held. More frequent examinations may be performed at the investigator's discretion, if medically indicated.

Table 7-2 WHO performance status 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 housework, 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

7.2.2.5 Laboratory evaluations

Central laboratories will be used for the analysis of scheduled hematology, biochemistry and other blood specimens collected as part of safety monitoring (as detailed in Table 7-1). Dipstick urinalysis will be performed locally, except in the case of any out of range parameter on scheduled local urinalysis, when a urine sample will be sent to central laboratory for further analysis. Laboratory values obtained during the Screening phase will be used to assess patient's eligibility. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1).

The site does not need to wait for the results of centrally-analyzed laboratory assessments when an immediate clinical decision needs to be made and in those cases locally unscheduled testing may be performed.

Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in a separate [Laboratory Manual].

[redacted]

Table 7-3 Clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hemoglobin, platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils [% or absolute])
Blood Chemistry	Albumin, ALT, AST, calcium (at screening calcium corrected for albumin in addition to calcium), creatinine, creatinine clearance, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, fasting glucose, phosphate (inorganic phosphorus), alkaline phosphatase, amylase, lipase, GGT
Urinalysis	Macroscopic Panel (Dipstick) (Color, bilirubin, Blood, Glucose, Ketones, Leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)
Pregnancy	At screening visit, serum pregnancy test At subsequent cycles, urinary pregnancy test (dipstick). If local requirements dictate otherwise, local regulations should be followed
Hormones (males only)	Testosterone (total and free), LH, FSH, sex hormone binding globulin (SHBG)
Coagulation	INR and pro-thrombin time (PT) or Quick Test

7.2.2.5.1 Hematology

Hematology assessments of the parameters listed in Table 7-3 will be tested as per the schedule of assessments (Table 7-1).

7.2.2.5.2 Clinical Chemistry

Blood chemistry assessments of the parameters listed in Table 7-3 will be tested as per the schedule of assessments (Table 7-1).

7.2.2.5.3 Urinalysis

Dipstick measurements will be performed as per Table 7-3 and according to the schedule of assessments. Any significant findings on dipstick will be followed up with microscopic evaluation as per Table 7-3.

7.2.2.5.4 Pregnancy and assessments of fertility

During screening, a serum pregnancy test will be completed (Day -28 to Day -1). On cycle 1 Day 1 prior to dosing and at subsequent cycles and at EOT, urinary pregnancy test (dipstick) will be performed. The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. Refer to Table 7-1. If local requirements dictate otherwise, local regulations should be followed.

Women who are determined not to be of child bearing potential before the study will only be tested at screening. When non-child bearing potential status is determined during the study, further pregnancy testing will not be continued. Women are considered post-menopausal if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), and otherwise not of child bearing potential if they have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential (such testing is not covered

[redacted]

as part of the study assessments). If local requirements dictate otherwise, local regulations should be followed.

The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. Refer to Table 7-1. If a positive pregnancy test is performed in between study visits, the patients must immediately notify the investigator.

Male patient must notify the investigator in case their partner is resulted pregnant during the treatment period.

7.2.2.5.5 Hormones

Testosterone (total and free), LH, FSH and steroid hormone binding globulin (SHBG) will be tested in male patients only and as per the schedule of assessments (Table 7-1).

7.2.2.5.6 Coagulation

International normalized ratio (INR) and prothrombin time (PT) or Quick Test will be measured at screening only.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as described in Table 7-4 and Table 7-5.

- At the screening visit in triplicate for all patients.
- At other defined time points as triplicate ECGs for first 15 patients run-in with extensive PK assessments during run-in period (Table 7-4) and patients with trough and sparse PK assessments (Table 7-5).

Baseline is defined as the pre-dose prior to 1st dose of LDK378.

All ECGs recorded for each time point will be transmitted electronically to a central laboratory and will be centrally reviewed by an independent reviewer in a blinded fashion in regards to treatment, time, and day (i.e., Cycle 1 Day1, Cycle 2 Day 1) identifiers. Any original ECG not transmitted electronically to the central laboratory should be forwarded for central review. Review of all ECGs from a particular patient should be performed by a single reader. The ECG lead for interval duration measurements should be pre-specified. Baseline and all subsequent ECGs should be based on the same lead.

Detailed instructions regarding the ECG collection will be provided to the investigators in a separate manual prior to the start of the study. ECGs should be performed within 30 minutes prior to the collection of PK sample. The triplicate ECGs should be taken approximately 2-4 minutes apart.

An ECG may be repeated at the discretion of the investigator at any time during the study and as clinically indicated. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site.

[redacted]

Table 7-4 ECG collection plan for patients with extensive PK assessment (in 15 patients who enrolled in PK run-in; triplicate ECGs)

Cycle	Day	Time	ECG Type
Screening	-28 to -1	Anytime	12 Lead
PK run-in	1	Pre-dose	12 Lead
PK run-in	1	Post-dose 4 hours (within 30 minutes before PK)	12 Lead
PK run-in	1	Post-dose 6 hours (within 30 minutes before PK)	12 Lead
PK run-in	2	Post-dose 24 hours (within 30 minutes before PK)	12 Lead
1	8	Pre-dose	12 Lead
1	8	Post-dose 2-4 hours (within 30 minutes before PK)	12 Lead
1	8	Post-dose 5-7 hours (within 30 minutes before PK)	12 Lead
1	15	Pre-dose	12 Lead
2	1	Pre-dose	12 Lead
2	1	Post-dose 4 hours (within 30 minutes before PK)	12 Lead
2	1	Post-dose 6 hours (within 30 minutes before PK)	12 Lead
2	1	24 hours post-dose of C2D1 (Pre-dose on C2D2)	12 Lead
3	1	Pre-dose	12 Lead
4	1	Pre-dose	12 Lead
5	1	Pre-dose	12 Lead
6 and subsequent cycles	1	Pre-dose	12 Lead
EOT	1	Pre-dose	12 Lead

Table 7-5 ECG collection plan for patients with sparse PK assessment (triplicate ECGs)

Cycle	Day	Time	ECG Type
Screening	-28 to -1	Anytime	12 Lead
1	1	Pre-dose	12 Lead
1	1	Post-dose 2-4 hours (within 30 minutes before PK)	12 Lead
1	1	Post-dose 5-7 hours (within 30 minutes before PK)	12 Lead
1	1	24 hours post-dose of C1D1 (Pre-dose on C1D2)	12 Lead
1	8	Pre-dose	12 Lead
1	8	Post-dose 2-4 hours (within 30 minutes before PK)	12 Lead
1	8	Post-dose 5-7 hours (within 30 minutes before PK)	12 Lead
1	15	Pre-dose	12 Lead
2	1	Pre-dose	12 Lead
2	1	Post-dose 4 hours (within 30 minutes before PK)	12 Lead
2	1	Post-dose 6 hours (within 30 minutes before PK)	12 Lead
3	1	Pre-dose	12 Lead
4	1	Pre-dose	12 Lead
5	1	Pre-dose	12 Lead
6 and subsequent cycles	1	Pre-dose	12 Lead
EOT	1	Pre-dose	12 Lead

Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with Novartis prior to enrolling the patient in the study. New or worsened clinically

[redacted]

significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.3 Pharmacokinetics

Pharmacokinetic blood collection plan

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 (Table 7-6). Additional patients may be enrolled in the study with PK run-in period in case PK profiles from some of the enrolled patients are deemed not evaluable due to early discontinuation from the study or due to vomiting events on the day of PK sampling. 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 (Table 7-7).

Meal records will be collected on PK run-in period Day 1 for the first 15 enrolled patients. Meal records will also be collected for all patients on Cycle 1 Day 1, Cycle 1 Day 8 and Cycle 2 Day 1. The start and end time of meals will be recorded. Complete dosing information, including the date and time of actual blood draw and time of the last study drug dose prior to the sampling, should be obtained on all sampling days and recorded on the PK eCRF and/or CRO requisition form(s). An additional blood sample (unscheduled) will be collected in the event that a patient experiences an AE which requires either dose modification or premature termination from the study medication.

Table 7-6 Pharmacokinetic blood collection for LDK378 extensive PK assessment (in 15 patients who enrolled in PK run-in)

Dose Reference Identification (ID)		PK sample number	Scheduled time points (hours)			
Dose ID following PK sampling	Dose ID prior to PK sampling		Cycle	Day	Scheduled time (hours)	Description
1		1	PK run-in	1	0 hr [a]	Pre-dose
1		2	PK run-in	1	0.5 hr ± 10 min	Post-dose
1		3	PK run-in	1	1 hr ± 15 min	Post-dose
1		4	PK run-in	1	2 hr ± 15 min	Post-dose
1		5	PK run-in	1	3 hr ± 15 min	Post-dose
1		6	PK run-in	1	4 hr ± 15 min	Post-dose
1		7	PK run-in	1	6 hr ± 15 min	Post-dose
1		8	PK run-in	1	8 hr ± 15 min	Post-dose
1		9	PK run-in	2	24 hr ± 120 min	Post-dose
1		10	PK run-in	3	48 hr ± 120 min	Post-dose
1		11	PK run-in	4	72 hr ± 120 min	Post-dose
1		12	PK run-in	5	96 hr ± 120 min	Post-dose
1		13	1	1	0 hr [a]	Pre-dose of Cycle 1 Day 1 (i.e. 120 hr post-dose in PK run-in)

[redacted]

Dose Reference Identification (ID)		PK sample number	Scheduled time points (hours)			
Dose ID following PK sampling	Dose ID prior to PK sampling		Cycle	Day	Scheduled time (hours)	Description
2	111 [b]	14	1	8	0 hr [a]	Pre-dose
2		15	1	8	2-4 hr	Post-dose
2		16	1	8	5-7 hr	Post-dose
3	112 [b]	17	1	15	0 hr [a]	Pre-dose
4	113 [b]	18	2	1	0 hr [a]	Pre-dose
4		19	2	1	1 hr ± 15 min	Post-dose
4		20	2	1	2 hr ± 15 min	Post-dose
4		21	2	1	4 hr ± 15 min	Post-dose
4		22	2	1	6 hr ± 15 min	Post-dose
4		23	2	1	8 hr ± 15 min	Post-dose
4		24	2	1	24 hr ± 120 min	24 hr post-dose of C2D1 (i.e. Pre-dose on C2D2)
5	114 [b]	25	3	1	0 hr [a]	Pre-dose
6	115 [b]	26	4	1	0 hr [a]	Pre-dose
7	116 [b]	27	5	1	0 hr [a]	Pre-dose
8	117 [b]	28	6	1	0 hr [a]	Pre-dose
		3001 + [c]	NA	NA	Unscheduled [c]	Unspecified

[a] PK sample should be taken immediately prior to the next administration of LDK378.
[b] Dose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample
[c] Sample numbers for any unscheduled blood collection for LDK378 will start with 3001.

Table 7-7 Pharmacokinetic blood collection for LDK378 sparse PK assessment

Dose Reference Identification (ID)		PK sample number	Scheduled time points (hours)			
Dose ID following PK sampling	Dose ID prior to PK sampling		Cycle	Day	Scheduled time (hours)	Description
11		301	1	1	0 hr [a]	Pre-dose
11		302	1	1	2-4 hr	Post-dose
11		303	1	1	5-7 hr	Post-dose
11		304	1	1	24 hr ± 120 min	24 hr post-dose of C1D1 (i.e. Pre-dose on C1D2)
12	101 [b]	305	1	8	0 hr [a]	Pre-dose
12		306	1	8	2-4 hr	Post-dose
12		307	1	8	5-7 hr	Post-dose
13	102 [b]	308	1	15	0 hr [a]	Pre-dose
14	103 [b]	309	2	1	0 hr [a]	Pre-dose
14		310	2	1	4 hr ± 15 min	Post-dose
14		311	2	1	6 hr ± 15 min	Post-dose
15	104 [b]	312	3	1	0 hr [a]	Pre-dose

[redacted]

Dose Reference Identification (ID)		PK sample number	Scheduled time points (hours)			
Dose ID following PK sampling	Dose ID prior to PK sampling		Cycle	Day	Scheduled time (hours)	Description
16	105 [b]	313	4	1	0 hr [a]	Pre-dose
17	106 [b]	314	5	1	0 hr [a]	Pre-dose
18	107 [b]	315	6	1	0 hr [a]	Pre-dose
		1001 + [c]	NA	NA	Unscheduled [c]	Unspecified

[a] PK sample should be taken immediately prior to the next administration of LDK378.
[b] Dose reference IDs with three digits refer to the dose administered and dosing time of the last dose prior to collection of the corresponding PK sample
[c] Sample numbers for any unscheduled blood collection for LDK378 will start with 1001.

At the specified time points detailed in Table 7-4 and Table 7-5, 2 mL of blood (per sample) will be collected for the measurement of the plasma concentrations of LDK378. All blood samples will be taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. Complete instructions for sampling processing, handling and shipment will be provided in the [Laboratory Manual]. All samples should be packed carefully as per the instructions in the manual, ensuring sufficient dry ice is used to keep samples frozen during shipment. Sample labels will include the following information: protocol number, subject ID, study day, actual date and time of blood collection, aliquot/matrix. Additional information may be added. A list of samples, including the date, subject number, and the time of sampling should be included in the shipment. Any missing samples should be indicated on the list. Residual plasma samples from this study may also be used for exploratory analysis to further characterize the PK of LDK378 and all of its metabolite(s). This may include using leftover samples for protein binding analysis or metabolite profiling (e.g., other metabolites and markers for metabolic enzyme activity such as 4- beta hydroxyl cholesterol levels), if there is sufficient sample remaining.

7.2.3.1 Analytical method

The plasma samples from all patients will be assayed for LDK378 concentrations, using a validated liquid chromatography-tandem mass spectrometry assay (LC-MS/MS). Values below the lower limit of quantification (LLOQ) of approximately 1.0 ng/mL or lower will be reported as 0.00 ng/mL. Missing values will be labeled accordingly.

[redacted]

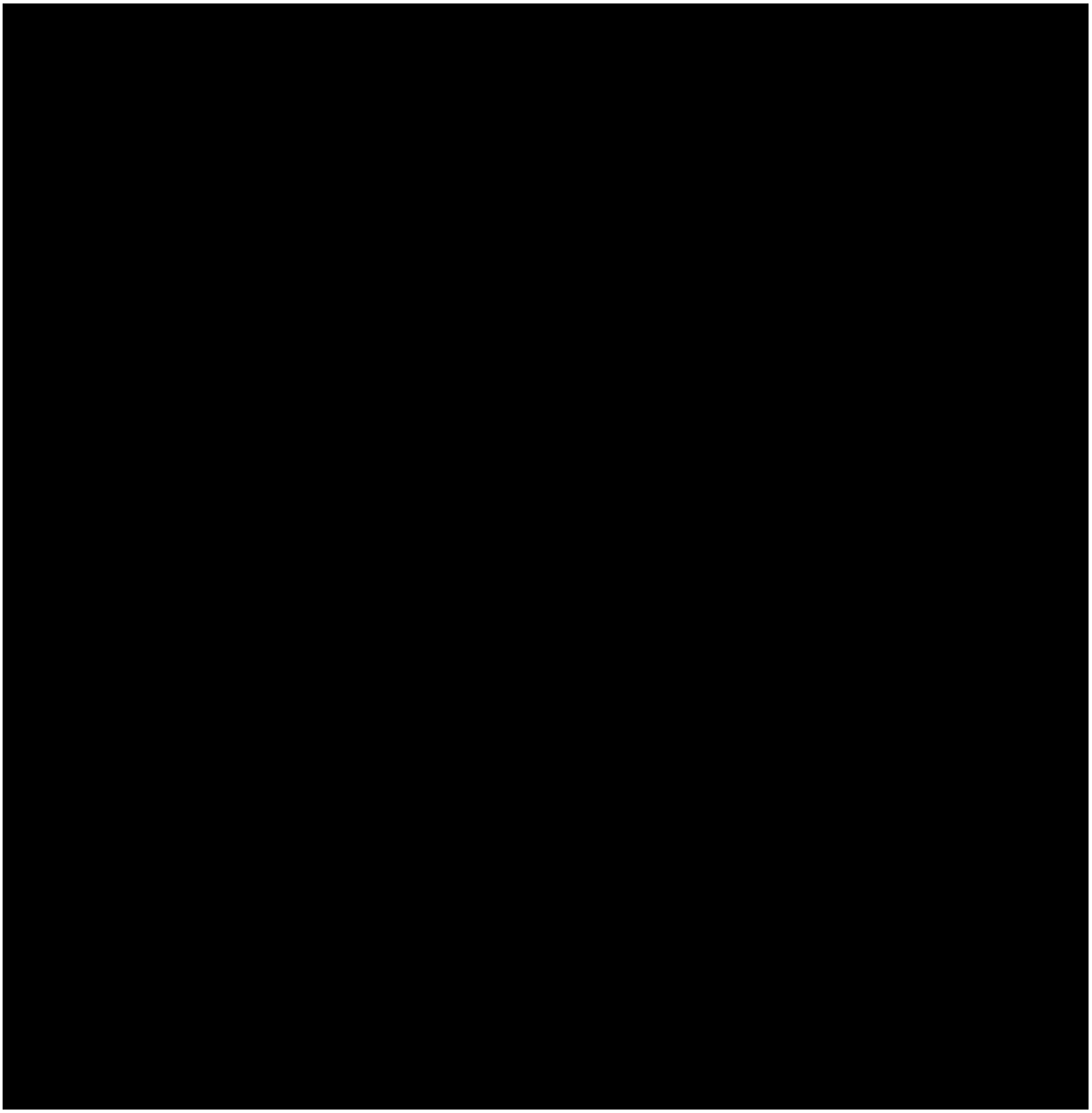
[redacted]

7.2.5 Resource utilization

Direct collection of health care resource utilization (HCRU) data (such as occurrences of hospitalization) is not planned for this study, but may be explored based on data contained within the SAEs eCRF.

[redacted]

[redacted]



8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

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

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events CRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF. Adverse event monitoring should be continued for at least 30 days (or 5 half-lives, whichever is longer) following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (dated 14 June 2010). If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death eCRF.

Abnormal laboratory values or test results occurring after signing the ICF constitute adverse events only if they induce clinical signs and symptoms, or require therapy, (e.g., any hematologic abnormality that requires transfusion of hematological stem cell support) or changes in medication(s) are considered clinical significant and should be recorded on the Adverse Event eCRF under signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinical significant (e.g. cause study discontinuation or constitute in and of itself a Serious Adverse Event) should be recorded on the Adverse Events eCRF.

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

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

[redacted]

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

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

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors or as per Cheson's guidelines for hematological malignancies), should not be reported as a serious adverse event.

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator’s discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

8.1.3 Adverse events of special interest

[redacted]

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

[redacted]

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Note that hospitalizations for the following reasons should not be reported as serious adverse events:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
- Note that treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE given above is not a serious adverse event

8.2.2 Reporting

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

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

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the oncology Novartis Drug Safety and Epidemiology (DS&E) department.

The telephone and telefax number of the contact persons in the local department of Drug Safety and Epidemiology (DS&E), specific to the site, are listed in the investigator folder

[redacted]

provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same contact(s) to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the [Investigator's Brochure] or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis Drug Safety and Epidemiology (DS&E) department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

8.3 Emergency unblinding of treatment assignment

Not applicable. This is an open-label study.

8.4 Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis immediately (within 24 hours) of learning of its occurrence. Patients who become pregnant during the trial must be withdrawn. The pregnancy will be followed up from the estimated date of delivery plus 3 months to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology Novartis DS&E. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment. A pregnancy outcome informed consent will be provided by Novartis. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving study treatment and up to 3 months after treatment has been stopped.

[redacted]

If a pregnancy occurs while on study treatment, the newborn will be followed for at least 3 months.

8.5 Warnings and precautions

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

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

A Steering Committee (SC), comprised of investigators in NSCLC management from the study, will be formed prior to initiation of the trial. The purpose of the SC is to provide overall guidance regarding design of the study, conduct and execution of the trial to include (but not limited to) safety, accrual and contribution to scientific input for publications.

Responsibilities of the SC and communication flow between, SC and Novartis will be included in the SC charter document.

9 Data collection and management

9.1 Data confidentiality

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

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

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

The data collection system for this study uses built-in security features to encrypt all data for transmission in both directions, preventing unauthorized access to confidential participant information. Access to the system will be controlled by a sequence of individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

[redacted]

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

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

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

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan.

9.3 Data collection

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

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

Radiological and photography data will be acquired by the sites and interpreted locally.

[redacted]

[redacted]

All ECGs will be transmitted electronically to a central laboratory and will be centrally reviewed by an independent reviewer. Any original ECG not transmitted electronically to the central laboratory should be forwarded for central review.

[redacted]

PK [redacted] samples drawn during the course of the study will be collected from the investigator sites and analyzed by a Novartis assigned laboratory or contracted central laboratories. The site staff designated by the investigator will enter the information required by the protocol onto the PK [redacted] Collection eCRFs, [redacted] as well as the designated laboratory's requisition forms that will be printed on 2-part paper. One copy of the requisition form will be forwarded to the central laboratory along with the corresponding samples with required information (including study number, subject ID, etc.) and the other copy will be retained by the site. The field monitor will review the relevant eCRFs for accuracy and completeness and will work with the site staff to adjust any discrepancies as required. The field monitor will also review the requisition forms for completeness. [redacted]

9.4 Database management and quality control

EDC is used for the study. Novartis personnel (or a designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Samples and/or data relating to PK samples, [redacted], ECGs and imaging will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

[redacted]

Enrollment will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor(s), who will also manage the database. The data will be sent electronically to Novartis personnel (or a designated CRO).

At the conclusion of the study, the occurrence of any protocol deviations will be determined. After these actions have been completed and the data has been verified to be complete and accurate, the database will be declared locked and the data available for data analysis. Authorization is required prior to making any database changes to locked data, by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical Development.

After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

10 Statistical methods and data analysis

The data from all participating centers in this protocol will be combined. Novartis and/or a designated CRO will perform all analyses. Any data analyses performed independently by any investigator should be submitted to Novartis before publication or presentation.

10.1 Analysis sets

10.1.1 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.

Patients who were screened but never started treatment will be listed.

10.1.2 Safety Set

The Safety Set consists of all patients who receive at least one dose of LDK378.

10.1.3 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 before that time), and no major protocol deviations.

All major protocol deviations leading to exclusion from the PPS will be detailed in the Reporting and Analysis Plan (RAP).

10.1.4 Dose-determining Analysis Set

Not applicable.

[redacted]

10.1.5 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set (PAS) consists of all patients who receive at least one dose of LDK378 and provide at least one evaluable PK sample.

The definition of an evaluable PK blood sample will be further specified in the RAP.

10.1.6 Other analysis Sets

All exploratory analyses intended to be discussed in the CSR will be defined in the RAP. Additional analyses may be performed on a program or company level. These will be planned and reported separately from this study.

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data including disease characteristics will be summarized descriptively for all patients for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. All demographic data will be listed in detail.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The Safety Set will be used for all medication data summaries and listings unless otherwise specified.

10.3.1 Study Treatment

The actual dose and duration of exposure in days to LDK378 as well as the dose intensity (computed as the ratio of total dose received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration), will be listed and summarized. Dose changes and dose interruptions (including the reasons for these) will be listed and summarized.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized.

10.4 Primary objectives

- To characterize the PK profile of LDK378 in Chinese adult patients with ALK-rearranged NSCLC following single and multiple once daily oral doses of LDK378.
- To assess safety and tolerability of LDK378 at 750 mg once daily dose in Chinese adult patients with ALK-rearranged locally advanced or metastatic NSCLC.

[redacted]

10.4.1 Variable

10.4.1.1 To characterize PK profile of LDK378

LDK378 PK parameters, including but not limited to AUClast, AUC0-24h, AUCinf, Cmax, Tmax, Lambda z, terminal T1/2, T1/2,acc, Racc, CL/F (or CLss/F at steady state) and Vz/F, as appropriate will be derived from the 15 patients who participated in the PK run-in period prior to a treatment period of continuous daily dosing.

10.4.1.2 To assess safety and tolerability of LDK378

Adverse events, vital signs, ECGs and laboratory abnormalities

10.4.2 Statistical hypothesis, model, and method of analysis

10.4.2.1 To characterize PK profile 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 (Table 7-6). Additional patients may be enrolled in the study with PK run-in period in case PK profiles from some of the enrolled patients are deemed not evaluable due to early discontinuation from the study or due to vomiting events on the day of PK sampling. 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 (Table 7-7).

Pharmacokinetic parameters of LDK378, including, but not limited to the following detailed in Table 10-1, will be calculated from the individual concentration-time profile obtained following the administration of LDK378. These PK parameters will be estimated, as appropriate. The non-compartmental method will be used on Phoenix WinNonlin (Version 6.2 Pharsight, Mountain View, CA).

Table 10-1 Noncompartmental pharmacokinetic parameters

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

[redacted]

Using the PAS, summary statistics (n, mean, SD, coefficient of variation (CV) for mean, geometric mean, CV for geometric mean, median, minimum and maximum) will be presented for concentration versus time profiles of LDK378. 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 mean and individual concentration versus time profiles of LDK378 will be displayed graphically for full PK profile and trough collections.

Summary statistics including n, mean, SD, CV for mean, geometric mean, CV for geometric mean, median, minimum and maximum will be presented for all PK parameters with the exception of Tmax. For Tmax, median, minimum and maximum will be presented for patients in the PAS with extensive PK assessment. [redacted]

The PK parameters and concentration data will be listed.

10.4.2.2 To assess safety and tolerability of LDK378

Please refer to Section 10.5.3.

10.4.3 Handling of missing values/censoring/discontinuations

Concentration values below the lower limit of quantitation (LLOQ) will be displayed in listings as zero with a footnote to explain and handled as zero in any calculations of summary statistics, but handled as missing for the calculation of the geometric means and their CV. Any missing PK concentration data will not to be imputed.

10.4.4 Supportive analyses

Not applicable.

10.5 Secondary objectives

All efficacy assessments (ORR, DOR, DCR, TTR, OIRR, PFS) will be analyzed as per investigator assessment. Confirmation of response is required for all response endpoints, as per RECIST 1.1. ORR and OIRR as assessed by BIRC will be the basis of supportive analyses.

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

10.5.1 Key secondary objective

- To evaluate anti-tumor activity of LDK378 in terms of ORR

10.5.1.1 Endpoint for key secondary objective

ORR is defined as the proportion of patients with a best overall confirmed response of CR or PR, as assessed per RECIST 1.1 by the investigator.

- 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.

[redacted]

- Patients with a best overall response of 'Unknown' or 'Not Assessed' per RECIST 1.1 will be considered as non-responders in estimating the ORR.
- 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.

10.5.1.2 Analysis for key secondary objective

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.

10.5.2 Other secondary efficacy objectives

- To evaluate efficacy endpoints as assessed by investigator: duration of response (DOR), disease control rate (DCR), time to response (TTR), overall intracranial response rate (OIRR) and progression free survival (PFS).
- To evaluate efficacy endpoints as assessed by BIRC: ORR.
- To evaluate overall survival (OS).

10.5.2.1 Endpoint and analysis for other secondary objectives

Duration of response

Among patients with a confirmed response (PR or CR) per RECIST 1.1, duration of response (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. DOR will be listed by patient and described using Kaplan-Meier curves and relevant statistics. Censoring rules for DOR follow those for PFS below.

Disease control rate

The disease control rate (DCR), defined as the proportion of patients with best overall response of CR, PR, or SD per RECIST 1.1 will be estimated and the 95% CI based on the exact binomial distribution will be provided.

Time to response

Time to response (TTR) is defined as the time from the date of the first dose of LDK378 to first documented response (CR or PR, which must be confirmed subsequently) per RECIST 1.1 for patients with a confirmed PR or CR. TTR will be described using appropriate summary statistics.

Progression-free survival

Progression-free survival (PFS) is defined as the time from the date of first dose of LDK378 to the date of first documented disease progression per RECIST 1.1 or death due to any cause.

A patient who has not progressed or died at the date of the analysis or when he/she receives any further anticancer therapy in the absence of disease progression will be censored at the time of the last adequate tumor evaluation before the earlier of the cut-off date or the

[redacted]

anticancer therapy date. By default, if disease progression or death is documented after one single missing tumor evaluation, the actual event date of disease progression/death will be used for the PFS event date. If disease progression or death is documented after two or more missing tumor evaluations, the PFS time of these patients will be censored at the date of the last adequate tumor evaluation without PD.

PFS assessed by the investigators will be described using Kaplan-Meier methods and appropriate summary statistics.

Overall survival

Overall survival (OS) is defined as the time from the date of first dose of LDK378 to the date of death due to any cause. OS time for patients who are alive at the end of the study or are lost to follow-up will be censored at the date of last contact.

OS will be described using Kaplan-Meier methods and appropriate summary statistics.

Overall intracranial response rate (OIRR)

OIRR is calculated based on response assessments in the brain for patients having measurable brain metastases at baseline (i.e. at least one target lesion in the brain). OIRR is defined as the ORR based on target and non-target lesions in the brain and 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.

ORR and OIRR will also be assessed by BIRC and be the basis of supportive analysis.

10.5.3 Safety objectives

10.5.3.1 Analysis set and grouping for the analyses

For all safety analyses, the Safety Set will be used.

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

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

The safety summary tables will include assessments from the on-treatment period, unless otherwise specified. Shift tables or change from baseline summaries will use data from the pre-treatment period for baseline calculations. Further details will be included in the Reporting and Analysis Plan (RAP).

[redacted]

10.5.3.2 Adverse events (AEs)

Summary tables for adverse events (AEs) will include only AEs observed during the on-treatment period. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment and after the on-treatment period will be flagged.

The incidence of AEs will be summarized by system organ class and or preferred term, maximum severity (based on CTCAE grades v4.03), and relation to study treatment.

Clinically notable adverse events (CNAE) categories will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment.

CNAEs will be defined at the project level and may be regularly updated based on emergent data. For each specified category, number and percentage of patients with at least one event per category will be summarized.

10.5.3.3 Laboratory abnormalities

For laboratory tests covered by the CTCAE version 4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For some cases (e.g. white blood cell differentials), the lower limits of normal ranges used in CTCAE definitions will have to be replaced by a clinical meaningful limit expressed in absolute counts.

For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

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

- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.

All laboratory data will be listed with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory toxicities).

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

[redacted]

10.5.3.4 Other safety data

Other safety data collected will be listed and summarized using descriptive statistics as appropriate. Notable values may be flagged. Notable/Abnormal values for safety data will be further specified in the RAP and will be used for shift tables.

Analyses will be performed on the safety set.

ECG

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

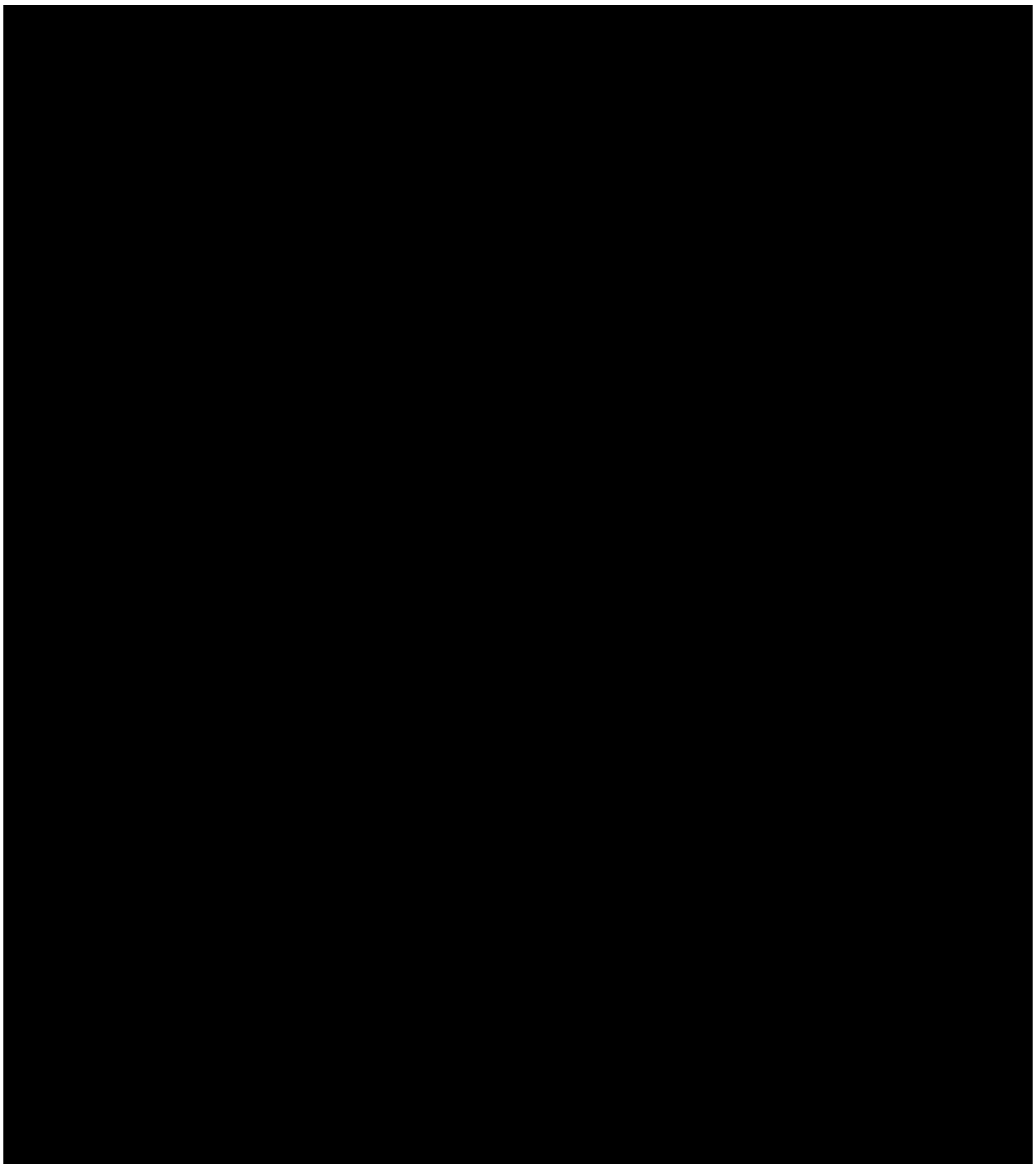
Vital signs

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline and change from baseline to worst post-baseline time points.

10.5.3.5 Tolerability

Tolerability will be summarized in terms of dose reductions or drug interruption due to an AE.

[redacted]



10.8 Interim analysis

An interim analysis will be performed after the first 30 patients enrolled have completed at least 16 weeks (4 cycles) of treatment with LDK378 or have discontinued earlier. The interim analysis will focus on full pharmacokinetics profile, safety and preliminary efficacy, including but not limited to:

- Pharmacokinetics: PK analysis will be performed. Plasma concentration of LDK378, and PK parameters for patients with extensive PK assessment 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.

Details of the analysis will be defined in RAP.

The primary clinical study report (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. The additional data for any patients continuing to receive study treatment, as allowed by the protocol, will be further summarized in a report once these patients completed the study (addendum of the clinical study report).

10.9 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. [redacted]

10.10 Power for analysis of key secondary variables

The study is not powered for formal hypothesis testing. However, with a total of 100 patients, if the observed ORR (key secondary endpoint) is 45% (45 responders in 100 treated patients), this will result in an exact binomial 90% CI of - [36.5% ,53.7%].

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB) before study start. Prior to study start, the investigator is

[redacted]

required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent.

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

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

Women of child bearing potential should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

[redacted]

11.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.4.

11.5 Publication of study protocol and results

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

[redacted]

11.6 Study documentation, record keeping and retention of documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of subjects. As part of participating in a Novartis-sponsored study, each site will permit authorized representatives of the sponsor(s) and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

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

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

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

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

11.7 Confidentiality of study documents and patient records

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to Novartis. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

[redacted]

11.8 Audits and inspections

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

11.9 Financial disclosures

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

12 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

12.1 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations (e.g. UK requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

[redacted]

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[redacted]

14 Appendices

14.1 Appendix 1: List of prohibited concomitant medications and concomitant medications requiring caution for LDK378

Table 14-1 Prohibited medications that are strong inducers or inhibitors of CYP3A, or CYP3A substrates with narrow therapeutic index, or sensitive CYP2C substrates with narrow therapeutic index**

CYP2C9 substrates with narrow therapeutic index			
warfarin	Phenytoin		
CYP3A4/5 substrates with narrow therapeutic index			
astemizole*	diergotamine	pimozide	alfentanil
cisapride*	ergotamine	quinidine*	terfenadine*
cyclosporine	Fentanyl	tacrolimus	sirolimus
Strong CYP3A4/5 inhibitors			
Macrolide antibiotics:	**Antivirals:**	**Antifungals:**	**Others:**
clarithromycin	Indinavir	itraconazole	conivaptan
telithromycin	Lopinavir	ketoconazole	elvitegravir
troleandomycin	Nelfinavir	posaconazole	mibefradil
	Ritonavir	voriconazole	nefazodone
	saquinavir		
	Tipranavir		
Strong CYP3A/5 inducers			
avasimibe	carbamazepine	phenobarbital	phenytoin
rifabutin	Rifampin	St. John's wort	

* Compounds with risk of QT prolongation
For an updated list of CYP2C substrates, CYP3A substrates, inhibitors and inducers, please reference the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database.

**Sensitive substrates: Drugs that exhibit an AUC ratio (AUCi/AUC) of 5-fold or more when co-administered with a known potent inhibitor.

Substrates with narrow therapeutic index (NTI): Drugs whose exposure-response indicates that increases in their exposure levels by the concomitant use of potent inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

[redacted]

Table 14-2 List of medications to be used with caution

CYP2C9 substrates			
losartan	Irbesartan	diclofenac	ibuprofen
piroxicam	tolbutamide	glipizide	acenocoumarol
celecoxib	sulfamethoxazole	tolbutamide	torsemide
CYP3A4/5 substrates			
dronedarone	capravirine	aripiprazole	simvastatin
alprazolam	Ritonavir	haloperidol	quinine
diazepam	Telaprevir	imatinib	tamoxifen
amlodipine	atorvastatin	nilotinib	tolvaptan
diltiazem	everolimus	methadone	trazodone
nifedipine		boceprevir	vincristine
nisoldipine	erythromycin	brecanavir	verapamil
nitrendipine			
Moderate CYP3A4/5 inhibitors			
ciprofloxacin	Darunavir	grapefruit juice	dronedarone
erythromycin	fosamprenavir	aprepitant	tofisopam
amprenavir	Diltiazem	casopitant	
atazanavir	Verapamil	cimetidine	
Moderate CYP3A4/5 inducers			
bosentan	Efavirenz	etravirine	modafinil
nafcillin	Ritonavir	talviraline	tipranavir
Proton pump inhibitors			
esomeprazole	lansoprazole	omeprazole	pantoprazole
rabeprazole			

The list of CYP2C9 and 3A4/5 substrates, 3A4/5 inhibitors and inducers is from the Novartis Oncology Clinical Pharmacology internal memo: drug-drug interactions (DDI) database, Oct 2010, which is compiled primarily from the Indiana University School of Medicine's "Clinically Relevant" Table (http://medicine.iupui.edu/flockhart/table.htm), the University of Washington's Drug Interaction Database (druginteractioninfo.org), and the FDA's "Guidance for Industry, Drug Interaction Studies".

[redacted]

Table 14-3 List of prohibited enzyme-inducing anti-epileptic drugs

Prohibited enzyme-inducing anti-epileptic drugs			
carbamazepine	Ethotoin	felbamate	fosphenytoin
phenobarbital	Phenytoin	primidone	topiramate

Table 14-4 List of prohibited QT prolonging drugs

Prohibited medications causing QTc prolongation			
Antiarrhythmic:	**Anticancer:**	**Antibiotic:**	**Antianginal:**
amiodarone	arsenic trioxide	azithromycin	bepridil
disopyramide	vavdetanib	clarithromycin*	**Antipsychotic:**
dofetilide	**Antihistamine:**	erythromycin*	chlorpromazine
flecainide	astemizole*	moxifloxacin	haloperidol*
ibutilide	terfenadine*	sparfloxacin	mesoridazine
procainamide	**Antimalarial:**	**Antinausea:**	pimozide
quinidine*	chloroquine	domperidone	thioridazine
sotalol	halofantrine	droperidol	**Opiate agonist:**
Antilipemic:	**Anti-infective:**	**GI stimulant:**	levomethadyl
probucol	pentamidine	cisapride*	methadone
Antidepressant:			
citalopram			

Please note: *CYP3A substrate
Source: Arizona Center for Education and Research on Therapeutics (CERT), Drugs that prolong the QT interval and/or induce Torsades de Pointes, http://.azcert.org/medical-pros/drug-lists/drug-lists.cfm

[redacted]

14.2 Appendix 2: Harmonization of efficacy analysis of solid tumor studies (RECIST 1.1)

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

Document type: TA Specific Guideline

Document status: Version 3.1: 29-Nov-2011
Version 3:0: 19-Oct-2009
Version 2:0: 18-Jan-2007
Version 1:0: 13-Dec-2002

Release date: 29-Nov-2011

List of contributors

Authors (Version 3.1): [redacted]

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Authors (Version 2): [redacted]

Authors (Version 1): [redacted]

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Glossary

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

14.2.1 Introduction

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

The efficacy assessments described in Section 14.2.2 and the definition of best response in Section 14.2.3.1 are based on the RECIST 1.1 criteria but also give more detailed instructions and rules for determination of best response. Section 14.2.3.2 is summarizing the "time to event" variables and rules which are mainly derived from internal discussions and regulatory consultations, as the RECIST criteria do not define these variables in detail. Section 14.2.4 of this guideline describes data handling and programming rules. This section is to be referred to in the RAP (Reporting and Analysis Plan) to provide further details needed for programming.

14.2.2 Efficacy assessments

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

14.2.2.1 Definitions

14.2.2.1.1 Disease measurability

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

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

For patients without measurable disease see Section 14.2.3.2.8.

Measurable lesions (both nodal and non-nodal)

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

[redacted]

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

14.2.2.1.2 Eligibility based on measurable disease

If no measurable lesions are identified at baseline, the patient may be allowed to enter the study in some situations (e.g. in Phase III studies where PFS is the primary endpoint). However, it is recommended that patients be excluded from trials where the main focus is on the Overall Response Rate (ORR). Guidance on how patients with just non-measurable disease at baseline will be evaluated for response and also handled in the statistical analyses is given in Section 14.2.3.2.8.

14.2.2.2 **Methods of tumor measurement - general guidelines**

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

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

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

[redacted]

- A change in methodology can be defined as either a change in contrast use (e.g. keeping the same technique, like CT, but switching from with to without contrast use or vice-versa, regardless of the justification for the change) or a change in technique (e.g. from CT to MRI, or vice-versa), or a change in any other imaging modality. A change in methodology will result by default in a UNK overall lesion response assessment. However, another response assessment than the Novartis calculated UNK response may be accepted from the investigator or the central blinded reviewer if a definitive response assessment can be justified, based on the available information.
- **FDG-PET:** can complement CT scans in assessing progression (particularly possible for 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  - Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  - No FDG-PET at baseline with a positive FDG-PET at follow-up:
  - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
  - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT are needed to determine if there is truly progression occurring at that Site (if so, the date of PD will be the date of the initial abnormal CT scan).
  - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Ultrasound:** When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- **Endoscopy and laparoscopy:** The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- **Tumor markers:** Tumor markers alone cannot be used to assess response. However, some disease specific and more validated tumor markers (e.g. CA-125 for ovarian cancer, PSA for prostate cancer, alpha-FP, LDH and Beta-hCG for testicular cancer) can be integrated as non-target disease. If markers are initially above the upper normal limit they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

[redacted]

- **Cytology and histology:** Cytology and histology can be used to differentiate between PR and CR in rare cases (i.e., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors). Cytologic confirmation of neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met the criteria for response or stable disease. Under such circumstances, the cytologic examination of the fluid collected will permit differentiation between response and stable disease (an effusion may be a side effect of the treatment) or progressive disease (if the neoplastic origin of the fluid is confirmed).
- **Clinical examination: Clinical lesions will only be considered measurable when they are** superficial (i.e., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

14.2.2.3 Baseline documentation of target and non-target lesions

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

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

Minimum target lesion size at baseline

- **Non-nodal target**: Non-nodal target lesions identified by methods for which slice thickness is not applicable (e.g. clinical examination, photography) should be at least 10 mm in longest diameter. See Section 14.2.2.1.1.
- **Nodal target**: See Section 14.2.2.1.1.

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

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

[redacted]

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

To assess tumor response, the sum of diameters for all target lesions will be calculated (at baseline and throughout the study). At each assessment response is evaluated first separately for the target (Table 14-5) and non-target lesions (Table 14-6) identified at baseline. These evaluations are then used to calculate the overall lesion response considering both the target and non-target lesions together (Table 14-7) as well as the presence or absence of new lesions.

14.2.2.4.1 Follow-up and recording of lesions

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

Non-nodal lesions

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

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

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

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

Nodal lesions

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

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

[redacted]

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

14.2.2.4.2 Determination of target lesion response

Table 14-5 Response criteria for target lesion

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

[1] SOD for CR may not be zero when nodal lesions are part of target lesions
[2] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR
[3] Methodology change See Section 14.2.2.2.

Notes on target lesion response

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

- The lesion is a new lesion, in which case the overall tumor assessment will be considered as progressive disease
- The lesion is clearly a reappearance of a previously disappeared lesion, in which case the size of the lesion has to be entered in the CRF and the tumor assessment will remain based on the sum of tumor measurements as presented in Table 14-5 above (i.e., a PD will be determined if there is at least 20% increase in the sum of diameters of **all** measured target lesions, taking as reference the smallest sum of diameters of all target lesions recorded at or after baseline with at least 5 mm increase in the absolute sum of the diameters). Proper documentation should be available to support this decision. This applies to patients who have not achieved target response of CR. For patients who have achieved CR, please refer to last bullet in this section.
- For those patients who have only one target lesion at baseline, the reappearance of the target lesion which disappeared previously, even if still small, is considered a PD.

[redacted]

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

[redacted]

14.2.2.4.3 Determination of non-target lesion response

Table 14-6 Response criteria for non-target lesions

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

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

Notes on non-target lesion response

- The response for non-target lesions is **CR** only if all non-target non-nodal lesions which were evaluated at baseline are now all absent and with all non-target nodal lesions returned to normal size (i.e. < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (i.e. ≥ 10 mm) the response can only be '**Non-CR/Non-PD**' unless any of the lesions was not assessed (in which case response is **UNK**) or there is unequivocal progression of the non-target lesions (in which case response is **PD**).
- **Unequivocal progression**: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of CR, PR or SD of target disease is therefore expected to be rare. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at baseline. If there is unequivocal progression of non-target lesion(s), then at least one of the non-target lesions must be assigned a status of "Worsened". Where possible, similar rules to those described in Section 14.2.2.4.2 for assigning PD following a CR for the non-target lesion response in the presence of non-target lesions nodal lesions should be applied.

14.2.2.4.4 New lesions

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

- If a new lesion is **equivocal**, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion

[redacted]

- If new disease is observed in a region which was **not scanned at baseline** or where the particular baseline scan is not available for some reason, then this should be considered as a PD. The one exception to this is when there are no baseline scans at all available for a patient in which case the response should be UNK, as for any of this patient's assessment (see Section 14.2.2.5).
- A **lymph node is considered as a "new lesion"** and, therefore, indicative of progressive disease if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase.
  FDG-PET: can complement CT scans in assessing progression (particularly possible for 'new' disease). See Section 14.2.2.2.

14.2.2.5 Evaluation of overall lesion response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response and presence of new lesions as shown below in Table 14-7.

Table 14-7 Overall lesion response at each assessment

Target lesions	Non-target lesions	New Lesions	Overall lesion response
CR	CR	No	CR[1]
CR	Non-CR/Non-PD[3]	No	PR
CR, PR, SD	UNK	No	UNK
PR	Non-PD and not UNK	No	PR1
SD	Non-PD and not UNK	No	SD[1, 2]
UNK	Non-PD or UNK	No	UNK[1]
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[1] This overall lesion response also applies when there are no non-target lesions identified at baseline.
[2] Once confirmed PR was achieved, all these assessments are considered PR.
[3] As defined in Section 14.2.2.4

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

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

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

14.2.3 Efficacy definitions

The following definitions primarily relate to patients who have measurable disease at baseline. Section 14.2.3.2.8 outlines the special considerations that need to be given to patients with no measurable disease at baseline in order to apply the same concepts.

[redacted]

14.2.3.1 Best overall response

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

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

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

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

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

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

- CR = at least two determinations of CR at least 4 weeks apart before progression where confirmation required or one determination of CR prior to progression where confirmation not required
- PR = at least two determinations of PR or better at least 4 weeks apart before progression (and not qualifying for a CR) where confirmation required or one determination of PR prior to progression where confirmation not required
- SD = at least one SD assessment (or better) > 6 weeks after randomization/start of treatment (and not qualifying for CR or PR).
- PD = progression ≤ 12 weeks after randomization/ start of treatment (and not qualifying for CR, PR or SD).
- UNK = all other cases (i.e. not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks)

[redacted]

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

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

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

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

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

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

- Investigator overall lesion response
- Central Blinded Review overall lesion response
- Novartis calculated overall lesion response (based on measurements from either Investigator or Central Review)

The primary analysis of the best overall response will be based on the sequence of investigator/central blinded review/calculated (investigator)/calculated (central) overall lesion responses.

Based on the patients' best overall response during the study, the following rates are then calculated:

[redacted]

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

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

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

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

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

14.2.3.2 Time to event variables

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

14.2.3.2.1 Progression-free survival

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

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

14.2.3.2.2 Overall survival

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

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

[redacted]

14.2.3.2.3 Time to progression

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

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

14.2.3.2.4 Time to treatment failure

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

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

14.2.3.2.5 Duration of response

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

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

[redacted]

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

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

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

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

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

14.2.3.2.6 Time to response

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

Although an analysis on the full population is preferred a descriptive analysis may be performed on the "responders" subset only, in which case the results should be interpreted with caution and in the context of the overall response rates, since the same kind of selection bias may be introduced as described for duration of response in Section 14.2.3.2.5. It is recommended that an analysis of all patients (both responders and non-responders) be performed whether or not a "responders only" descriptive analysis is presented. Where an inferential statistical comparison is required, then all patients should definitely be included in the analysis to ensure the statistical test is valid. For analysis including all patients, patients who did not achieve a response (which may have to be a confirmed response) will be censored using one of the following options.

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

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

[redacted]

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

Assessment date

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

Start dates

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

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

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

End dates

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

- Date of death (during treatment as recorded on the treatment completion page or during follow-up as recorded on the study evaluation completion page or the survival follow-up page).
- Date of progression is the first assessment date at which the overall lesion response was recorded as progressive disease.
- Date of last adequate tumor assessment is the date the last tumor assessment with overall lesion response of CR, PR or SD which was made before an event or a censoring reason occurred. In this case the last tumor evaluation date at that assessment is used. If no post-baseline assessments are available (before an event or a censoring reason occurred) the date of randomization/start of treatment is used.
- Date of next scheduled assessment is the date of the last adequate tumor assessment plus the protocol specified time interval for assessments. This date may be used if back-dating is considered when the event occurred beyond the acceptable time window for the next tumor assessment as per protocol (see Section 14.2.3.2.8).

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

- Date of discontinuation is the date of the end of treatment visit.
- Date of last contact is defined as the last date the patient was known to be alive. This corresponds to the latest date for either the visit date, lab sample date or tumor assessment date. If available, the last known date patient alive from the survival follow-up page is used. If no survival follow-up is available, the date of discontinuation is used as last contact date.

[redacted]

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

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

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

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

Although the text of the definitions described in the previous sections primarily relates to patients with measurable disease at baseline, patients without measurable disease should also be incorporated in an appropriate manner. The overall response for patients with measurable disease is derived slightly differently according to Table 14-8.

Table 14-8 Overall lesion response at each assessment: patients with non-target disease only

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

[1] As defined in Section 14.2.2.4.

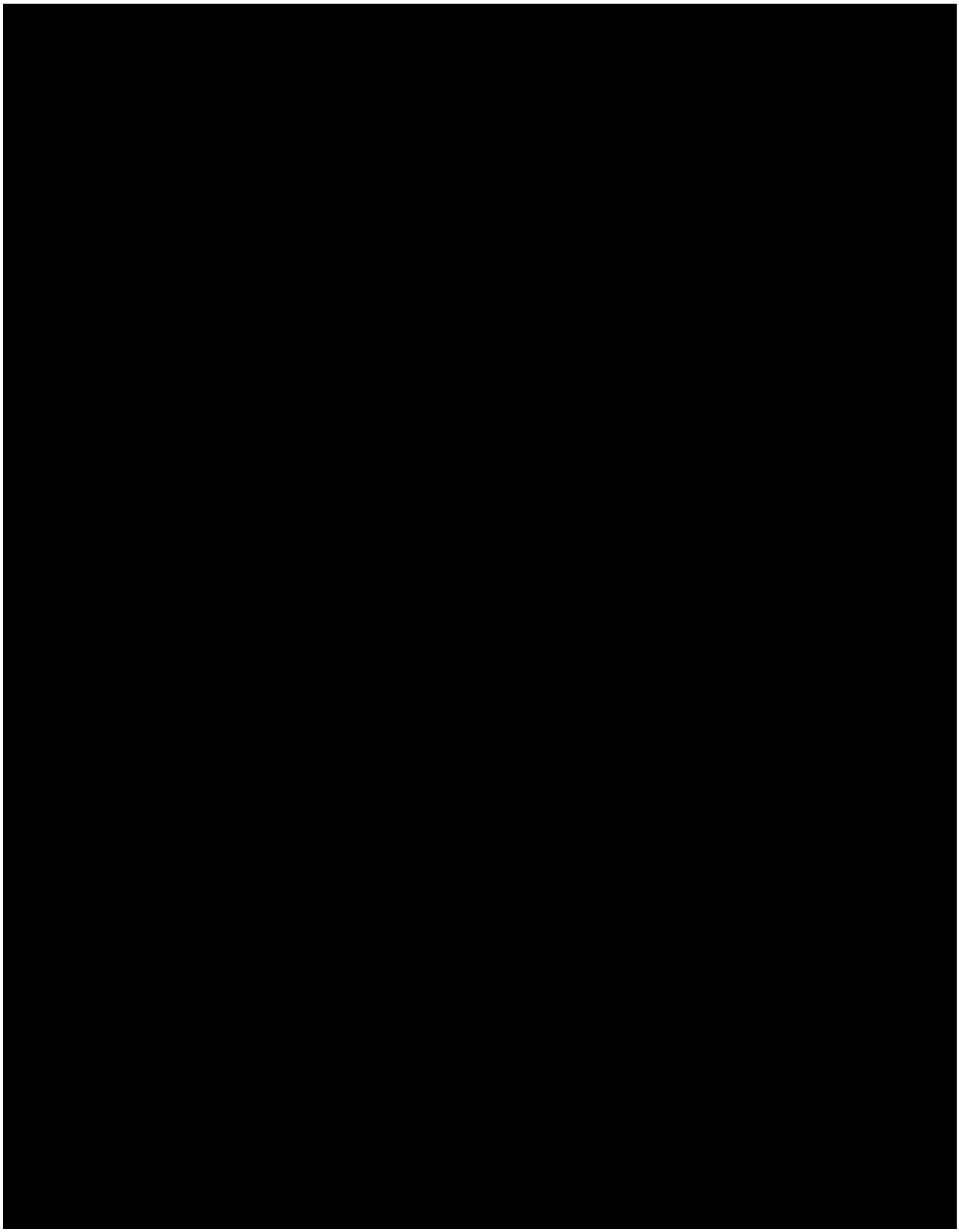
In general, the **non-CR/non-PD response** for these patients is considered equivalent to an SD response in endpoint determination. In summary tables for best overall response patients with only non-measurable disease may be highlighted in an appropriate fashion e.g. in particular by displaying the specific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

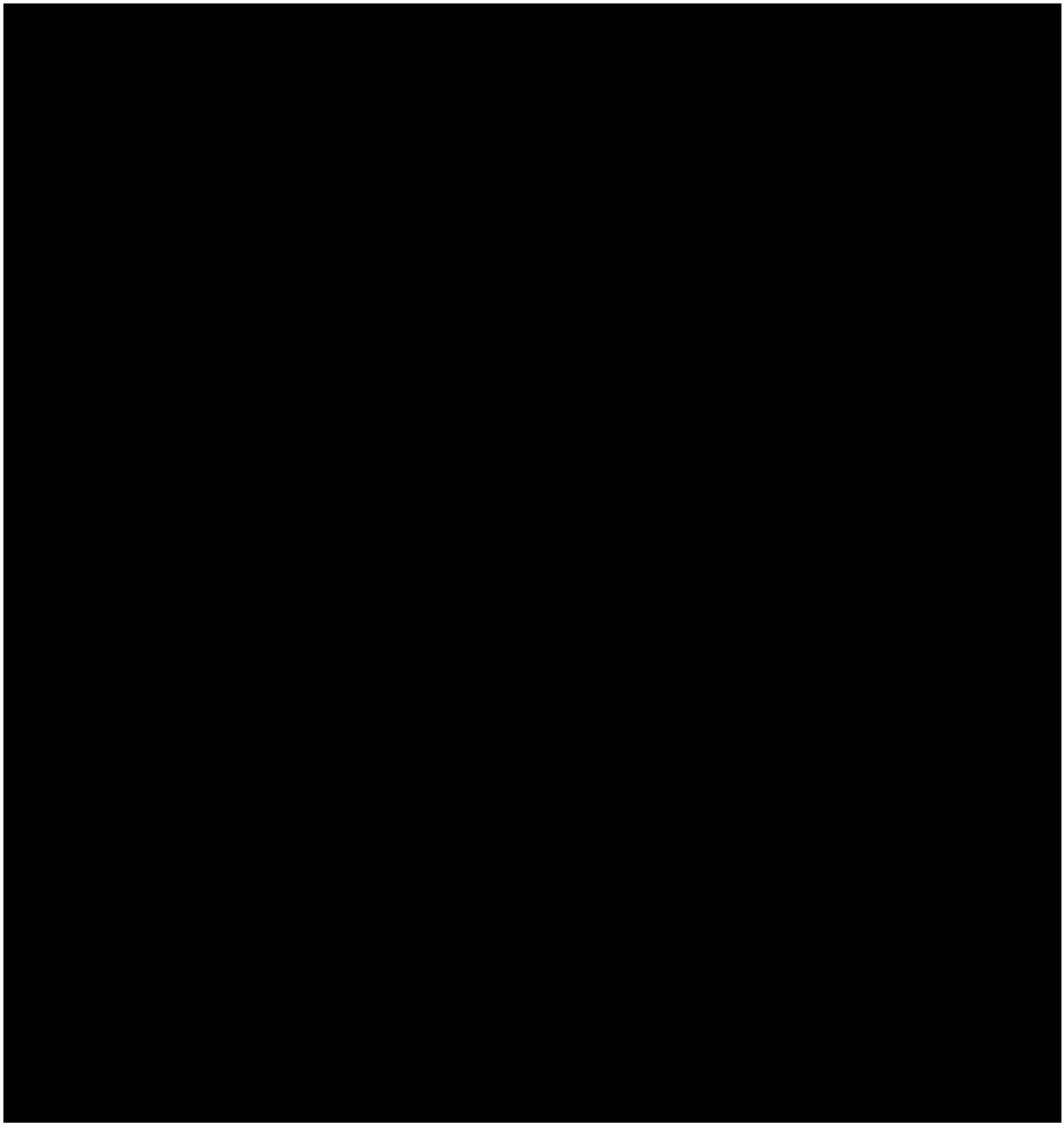
In considering how to incorporate data from these patients into the analysis the importance to each endpoint of being able to identify a PR and/or to determine the occurrence and timing of progression needs to be taken into account.

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

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

[redacted]





14.2.4 Data handling and programming rules

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

14.2.4.1 Study/project specific decisions

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

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

14.2.4.2 End of treatment phase completion

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

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

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

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

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

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

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

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

[redacted]

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

14.2.4.4 Medical validation of programmed overall lesion response

As RECIST is very strict regarding measurement methods (i.e. any assessment with more or less sensitive method than the one used to assess the lesion at baseline is considered UNK) and not available evaluations (i.e. if any target or non-target lesion was not evaluated the whole overall lesion response is UNK unless remaining lesions qualified for PD), these UNK assessments may be re-evaluated by clinicians at Novartis or external experts. In addition, data review reports will be available to identify assessments for which the investigators' or central reader's opinion does not match the programmed calculated response based on RECIST criteria. This may be queried for clarification. However, the investigator or central reader's response assessment will never be overruled.

If Novartis elect to invalidate an overall lesion response as evaluated by the investigator or central reader upon internal or external review of the data, the calculated overall lesion response at that specific assessment is to be kept in a dataset. This must be clearly documented in the RAP documentation and agreed before database lock. This dataset should be created and stored as part of the 'raw' data.

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

14.2.4.5 Programming rules

The following should be used for programming of efficacy results:

14.2.4.5.1 Calculation of 'time to event' variables

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

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

14.2.4.5.2 Incomplete assessment dates

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

If one or more investigation dates are incomplete but other investigation dates are available, this/these incomplete date(s) are not considered for calculation of the assessment date (and assessment date is calculated as outlined in Section 14.2.3.2.7). If all measurement dates have no day recorded, the 1st of the month is used.

[redacted]

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

14.2.4.5.3 Incomplete dates for last known date patient alive or death

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

14.2.4.5.4 Non-target lesion response

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

14.2.4.5.5 Study/project specific programming

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

14.2.4.5.6 Censoring reason

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

For survival the following censoring reasons are possible:

- Alive
- Lost to follow-up

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

- Ongoing without event
- Lost to follow-up
- Withdrew consent
- Adequate assessment no longer available*
- Event documented after two or more missing tumor assessments (optional, see Table 14-9)
- Death due to reason other than underlying cancer *(only used for TTP and duration of response)*
- Initiation of new anti-cancer therapy

*Adequate assessment is defined in Section 14.2.3.2.7. This reason is applicable when adequate evaluations are missing for a specified period prior to data cut-off (or prior to any other censoring reason) corresponding to the unavailability of two or more planned tumor assessments prior to the cut-off date. The following clarifications concerning this reason should also be noted:

[redacted]

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

14.2.5 References (available upon request)

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

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

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

FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, April 2005.

FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007.

Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. Cont Clin Trials; 9: 11-18.

Therasse P, Arbuck S, Eisenhauer E, et al (2000) New Guidelines to Evaluate the Response to Treatment in Solid Tumors, Journal of National Cancer Institute, Vol. 92; 205-16.

[redacted]

14.3 Appendix 3: ALK Immunohistochemistry

The population for this study includes adult Chinese patients with locally advanced or metastatic NSCLC harboring a confirmed ALK rearrangement, defined as positive using the FDA approved Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular Inc.) test and scoring algorithm (including positivity criteria) or positive as assessed by the CFDA approved immunohistochemistry (IHC) test (Ventana Medical Systems, Inc) using rabbit monoclonal primary antibody assay (D5F3) and associated scoring algorithm. If documentation of ALK rearrangement is not available as described above, a test to confirm ALK rearrangement must be performed using an archival tumor obtained at or since the time of diagnosis or a new tumor biopsy obtained prior to the first LDK378 dose. The test will be performed at a Novartis designated central laboratory (by IHC test using rabbit monoclonal primary antibody assay (D5F3), Ventana Medical Systems, Inc). Patients must wait for the result of the ALK rearrangement status before initiating treatment with LDK378.

Overview

The VENTANA anti-ALK (D5F3) Rabbit Monoclonal Primary Antibody (VENTANA anti-ALK (D5F3) IHC assay will be used to determine ALK IHC status and to select ALK-positive patients for enrollment in Study [CLDK378A2301]. The anti-ALK (D5F3) rabbit monoclonal antibody IHC assay is currently being developed by Ventana Medical Systems as a companion diagnostic to LDK378. For study CLDK378A2301, the VENTANA anti-ALK (D5F3) assay will be used for investigational purposes only. VENTANA anti-ALK (D5F3) is intended for laboratory use in the detection of the anaplastic lymphoma kinase (ALK) protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue stained with a VENTANA BenchMark XT® immunohistochemical (IHC) automated slide stainer. It is indicated as an aid in identifying patients eligible for treatment with LDK378.

Device Description

The VENTANA anti-ALK (D5F3) IHC assay is an automated IHC staining assay system comprising a pre-diluted, ready-to-use anti-ALK (D5F3) rabbit monoclonal primary antibody, the BenchMark® XT automated slide-staining platform, OptiView DAB detection kit, OptiView Amplification kit, Rabbit Monoclonal Negative Control Ig and VENTANA anti-ALK 2-in-1 cell line control slides. The reagents and the IHC procedure are optimized for use on the BenchMark XT® automated slide stainer, utilizing NexES software (Ventana System Software).

Scoring System

The IHC scoring system evaluates specific VENTANA anti-ALK (D5F3) staining in NSCLC tumor cells by the presence of a strong, granular, cytoplasmic staining pattern. Pathologists must rely on the Negative Reagent Control (NRC) slides to distinguish non-specific staining from specific ALK positivity. Samples must be assessed for morphological damage and the presence of viable tumor versus necrosis. Light, granular, cytoplasmic stippling in alveolar macrophages can occur on anti-ALK (D5F3) and/or NRC slides as an artifact of the detection system. This staining artifact should be noted on the Slide Evaluation Form comment field but

[redacted]

should NOT be interpreted as ALK-positive staining. Some background staining has also been observed on normal mucosa in NSCLC specimens, as well as in necrotic tumor areas; this staining also should not be interpreted as ALK-positive staining. Case slide sets failing to show specific staining of the case tissue with VENTANA anti-ALK (D5F3) as defined in the following table cannot be considered ALK-positive.

Table 14-10 Clinical Interpretation of VENTANA anti-ALK (D5F3) Staining

Clinical Interpretation	Staining Description
Positive for ALK	Presence of strong granular cytoplasmic staining in tumor cells (any percentage of positive tumor cells). Known staining artifacts should be excluded, including: light cytoplasmic stippling in alveolar macrophages, cells of neural origin (nerve and ganglion cells), glandular epithelial staining, and cells within lymphocytic infiltrate. Some background staining also may be observed within normal mucosa in NSCLC (including mucin) and in necrotic tumor areas, which also should be excluded from the clinical evaluation.
Negative for ALK	Absence of strong granular cytoplasmic staining in tumor cells.

[redacted]

14.4 Appendix 4: Cockcroft-Gault formula

Female:

$$GFR[ml/\min] = 0{,}85 \cdot \frac{(140 - age[y]) \cdot bodyweight[kg]}{72 \cdot serum\ creatinine\ [mg/dl]}$$

Male:

$$GFR[ml/\min] = \frac{(140 - age[y]) \cdot bodyweight[kg]}{72 \cdot serum\ creatinine\ [mg/dl]}$$

[redacted]