NOVARTIS

Clinical Development

LDK378

Clinical Trial Protocol CLDK378A2203 / NCT01685138

A phase II, multicenter, single-arm study of oral LDK378 in crizotinib naïve adult patients with ALK-activated non-small cell lung cancer

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List of abbreviations

AE	Adverse event
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
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
AUCtau	Area under the plasma (serum, or blood) concentration versus time curve from time zero to end of dosing period
AUClast	Area under the concentration-time curve from time zero to the last measurable concentration time
BIRC	Blinded Independent Review Committee
BLRM	Bayesian logistic regression model
CI	Confidence interval
CL	Clearance
DBP	Diastolic blood pressure
C_{max}	Maximum (peak) concentration of drug in plasma
C_{min}	Minimum (trough) concentration of drug in plasma
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRO	Contract Research Organization
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
D	Entered into database
DILI	Drug Induced Liver Injury
DLT	Dose limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
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
EOT	End of treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice

[redacted]

GGT	Gamma-glutamyl transpeptidase
HA	Health Authorities
HED	Human equivalent dose
Hgb	Hemoglobin
HSV	Herpes Simplex Virus
IB	Investigator's brochure
IC_{50}	Half maximal (50%) inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous(ly)
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
[redacted]	[redacted]
LFT	Liver function test
LH	Luteinizing hormone
LLN	Lower limit of normal
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
N/A	Not applicable
NCCN	National Comprehensive Cancer Center
NSCLC	Non-small cell lung cancer
OIRR	Overall intracranial response rate
ORR	Overall response rate
PD	Progressive disease
PFS	Progression-free survival
PI	Principal investigator
PK	Pharmacokinetics
PPS	Per-protocol set
PR	Partial response
QTc	Corrected QT interval
QTcF	Corrected QT interval using Fridericia formula
QD	*quaque diem*/once daily
R value	ALT/ALP in x ULN
R_{acc}	Accumulation ratio
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analysis
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

[redacted]

SHBG	Sex hormone binding globulin
SI units	Standard international units
SUSARs	Suspected unexpected serious adverse reactions
$t_{1/2}$	Elimination half-life associated with the terminal slope (lambda_z) of a semi logarithmic concentration-time curve (time).
TBIL	Total Bilirubin
TKIs	Tyrosine kinase inhibitors
T_{max}	The time to reach maximum plasma concentration
TTR	Time to response
ULN	Upper limit of normal
V_{ss}	Plasma volume of distribution
VATS	Video-assisted thoracic surgery
VEGF-A	Vascular endothelial growth factor-A
WHO	World Health Organization

[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biological samples	A biological specimen including , for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. 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
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (eg, q 21 days)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (ie, 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”
Subject 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
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, completion of treatment, etc.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
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 drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any combination or control drug(s)
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason;
Variable	A quantity subject to variation of values used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points
Withdrawal of consent	Withdrawal of consent 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

[redacted]

Protocol summary

Protocol number	CLDK378A2203
Title	A phase II, multicenter, single-arm study of oral LDK378 in crizotinib naïve adult patients with ALK-activated non-small cell lung cancer
Brief title	LDK378 in non-small cell lung cancer patients with ALK rearrangements who are crizotinib naïve
Sponsor and Clinical Phase	Novartis, Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	ALK+ NSCLC patients have only crizotinib as an effective ALK targeted treatment option and therefore novel ALK targeted therapies with activity against ALK+ NSCLC are needed. The available data indicate that LDK378 has substantial antitumor activity in patients with ALK rearranged NSCLC
Primary Objective and Key Secondary Objective(s)	Primary objective: To demonstrate the antitumor activity of LDK378, as measured by overall response rate (ORR) to LDK378 by investigator assessment Key secondary objectives: To evaluate response related endpoints as assessed by investigator and blinded independent review committee (BIRC): duration of response (DOR), disease control rate (DCR), time to response (TTR), overall intracranial response rate (OIRR); and to assess ORR by BIRC assessment
Secondary Objectives	Objective 1: To evaluate the safety profile of LDK378 Objective 2: To evaluate progression-free survival (PFS) Objective 3: To evaluate overall survival (OS)
Study design	This is a single-arm, open-label, two-stage multicenter, phase II study. Patients will be pre-screened for ALK positive status. Treatment with LDK378 at 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 as assessed by the investigator, if in the judgment of the investigator, there is evidence of clinical benefit. In these patients tumor assessment should continue as per the schedule of assessments until treatment with LDK378 is permanently discontinued. Patients who discontinue the study medication in the absence of progression will continue to be followed for tumor assessment until the time of PD as assessed by the investigator. The study will use a Simon's optimal two-stage design. Stage 1 will consist of 43 patients and their data up to 6 cycles of treatment unless a patient has discontinued treatment earlier or a confirmed response to treatment has been observed prior to completing 6 cycles. The trial will be stopped at Stage 1 if 16 or fewer responses are observed. If at the time that the last patient is enrolled to Stage 1 a minimum of 17 responses have not yet been observed, accrual may be temporarily suspended during the analysis of Stage 1. Stage 2 will include an additional 62 patients. The primary analysis will occur when all 105 patients have completed 6 cycles of treatment or discontinued treatment earlier.
Population	Male and female patients aged 18 or over with ALK-rearranged NSCLC. Patients must have received no prior crizotinib, and must be chemotherapy-naïve or have been treated with cytotoxic chemotherapy (up to 3 prior lines).

[redacted]

Inclusion criteria	• Histologically or cytologically confirmed diagnosis of stage IIIB or IV NSCLC that carries an ALK rearrangement, as per the FDA-approved Vysis ALK break-apart FISH assay (Abbott Molecular Inc.). • Age 18 years or older at the time of informed consent. • Patients must have stage IIIB or IV NSCLC. • Patients may have received up to 3 lines of cytotoxic chemotherapy to treat their stage IIIB or IV NSCLC • Patients who have been treated with chemotherapy must have progressed during or after the last chemotherapy regimen received prior to the first dose of LDK378 • Patients must have a tumor tissue sample available, preferably being a new biopsy but otherwise being an archival sample collected either at the time of diagnosis of NSCLC or any time since, for assessing ALK rearrangements using the FDA-approved Vysis ALK break-apart FISH assay. • Patients must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 2, except 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.
Exclusion criteria	• Prior treatment with crizotinib, or any other ALK inhibitor investigational agent, for NSCLC • Patients with known hypersensitivity to any of the excipients of LDK378. • 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. • History of carcinomatous meningitis. • Presence or history of a malignant disease other than NSCLC that has been diagnosed and/or required therapy within the past 3 years. • Clinically significant, uncontrolled heart disease.
Investigational and reference therapy	LDK378
Efficacy assessments	Tumor assessment by RECIST 1.1 as evaluated by investigator and by a BIRC
Safety assessments	• Hematology, biochemistry, urinalysis, coagulation, pregnancy test and hormones (males only) • ECG • Performance status • Vital signs • Adverse events
Other assessments	• Trough and sparse PK [redacted]

[redacted]

Data analysis	The cut-off date for the primary analysis of this trial will be the time when all 105 patients have completed 6 cycles of treatment or have discontinued treatment. The ORR per RECIST 1.1 by investigator assessment and by BIRC assessment will be estimated and the 90% confidence interval (CI) provided. If the true ORR is 50% (under the alternative hypothesis), approximately 105 patients are required to reject the null hypothesis of ORR ≤ 35% with a one-sided alpha of 0.05 based on Simon's optimal two-stage design. If 45 or more responses are seen in 105 total patients (estimated ORR of 42.9%), then the null hypothesis will be rejected and the trial declared positive. If the study is terminated early at the end of Stage 1, then the study will be considered to have failed to reject the null hypothesis. The uniformly minimum variance unbiased estimator (UMVUE) and the 90% CI from Atkinson and Brown (1985) will also be presented. DOR will be listed by patient and may be described using Kaplan-Meier methods and relevant statistics if appropriate. DCR and OIRR will be estimated and the 90% CI provided. TTR, PFS, and OS will be described using Kaplan-Meier methods and appropriate summary statistics. Adverse events and laboratory abnormalities will be summarized and listed.
Key words	ALK, NSCLC, LDK378

[redacted]

Amendment 4

Amendment rationale

As of the release date of this amendment the recruitment has been completed and 132 patients have been screened to the study. A total of 124 patients have been treated.

This amendment has been implemented to:

- Update the protocol to include follow up evaluations for hepatic toxicities and work-up guidelines for potential Drug Induced Liver Injury (DILI) cases in order to optimize the patient safety.
- Update the dose guidance modification for QTcF text to provide clarification on monitoring procedure.
- Update the guidance related to corticosteroids use
- Update of the definition of the End of Study
- 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 font for insertions.

The following sections were changed:

- List of abbreviations updated with commonly used abbreviations such as R value, TBIL, DILI, EBV, CMV, and HSV
- Section 4.3: the definition of the End of Study has been updated to allow patients' transition to othe clinical studies or to patient support programs
- Section 6.2.4.2: updated guidelines to monitor liver abnormalities for patients with transaminase increase combined with total bilirubin (TBIL) increase which may be indicative of potential DILI
- Table 6-3: updated dose modification guidelines to monitor Grade 3 QTc prolongation
- Section 6.3.1.1: updating corticosteroide use guidance and wording on increasing doses of corticosteroids use has been removed.
- Section 8.2.2: Updated reporting instructions.
- 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.

[redacted]

Amendment 3

Amendment rationale

As of the release date of this amendment the recruitment has been completed and 132 patients have been screened to the study. A total of 124 patients have been treated.

This amendment has been implemented to include availability of new safety data as presented in the Investigator's Brochure and to clarify sections of the protocol where additional guidance was required:

- Update of safety data in the protocol to match the Investigator's Brochure Edition 7 (released on 12 Jun 2014). The associated Informed Consent Form (ICF) has been updated separately to this protocol
- Update of the LDK378 dose modification and follow up of toxicities in case of elevations of pancreatic enzymes (lipase and/or amylase) 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
- An evaluation of the anticipated benefits and risks has been added to the protocol to comply with EU clinical trial regulations.
- Revision of sections 7.1.4, 7.1.5 and 7.1.6 related to study discontinuation to bring clarification and additional guidance regarding study treatment discontinuation and withdrawal of consent

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 font for insertions.

The following sections were changed:

- List of abbreviations updated with commonly used abbreviations such as GGT, ILD and NCCN
- Glossary of terms updated with definitions for biological samples, study drug discontinuation and withdrawal of consent
- Section 1.2.1.2.1: clinical safety and tolerability data updated to reflect data most recently available from ongoing study CLDK378X2101
- Section 1.2.1.1.3, Section 6.3.1.2: Updated nonclinical PK and metabolism data from recent studies. Evaluation of DDI potential was re-conducted for NDA submission. Using the 2012 FDA Draft Guidance "Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations" and the 2012 EMA "Guideline on the Investigation of Drug Interactions," the mechanistic static model determined that

[redacted]

the inhibitory potential of LDK378 is low for CYP2C8 and CYP2B6 (AUCR <1.25). As such, the sentence regarding LDK378 being a potent reversible inhibitor of CYP2C8 and CYP2B6 was removed

- Section 1.2.1.2.4: updated to reflect the most recently available food effect study data
- Section 1.3: added new section "Risks and benefits"
- 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
- Section 6.2.2: section updated with instructions that guidelines for follow-up of study drug related AEs or abnormal laboratory values must be followed as described in Section 6.2.4
- Section 6.2.3: clarification that dose reductions will be in 150 mg decrements per reduction and that once the dose of LDK378 has been reduced due to toxicity, it should not be re-escalated
- Table 6-3: updated to reflect the most recently available data where criteria for interruption and re-initiation of LDK378 treatment are now less stringent (such as allowing maintenance of dose level in the case of neutropenia Grade 3 and elevated ALT/AST Grade 2), while for other criteria, more stringent dose modifications have been introduced (such as for elevated ALT/AST Grade 2 and concurrent total bilirubin >2.0 xULN, pneumonitis all grades and QTC prolongation Grade 3). Criteria for interruption and re-initiation of LDK378 treatment for bradycardia, hyperglycemia and pancreatitis has been added to Table 6-3
- Section 6.2.4.2 and Table 6-4: updated guidelines to monitor liver abnormalities for patients with baseline liver metastases and elevated ALT/AST Grade 2
- Section 6.2.4.3: addition of guidelines for the follow-up of laboratory pancreatic abnormalitiesTable 6-4: addition of follow-up evaluations for pancreatic toxicities
- Section 6.2.4.6: updated safety data for hypophosphatemia
- Section 6.2.4.8: addition of guidelines for anticipated risks and safety concerns for the study treatment
- Section 6.3.1.1: clarification added when increasing doses of corticosteroids are used
- Section 6.3.1.2: updated CYP450 drug interactions with LDK378
- Section 6.3.1.4: updated with LDK378 dosing guidance in association to radiotherapy and surgical resection in order to align with program level language
- Section 6.3.2.1: addition of targeted therapy to other anticancer therapies
- 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
- Section 6.3.2.8: updated with most recent data on QTc prolongation from ongoing study CLDK378X2101
- Section 7.1.4: The title of the section is changed to reflect updated guidance on how to follow subjects who discontinue study treatment, either some or all of the visits, withdraw consent or are lost to follow-up
- Section 7.1.4.2: added new section 'Withdrawal of consent'
- Section 7.1.6: added new section 'Lost to follow–up'

[redacted]

- Section 4.1 and 7.2.1.2: deletion of the start of new anti-cancer therapy as an allowable reason to stop collecting tumor assessments to enable sensitivity analysis of PFS following a pure intent-to-treat principle where start of new antineoplastic therapy does not result in censoring for PFS
- Table 7-3:clinical laboratory parameters collection plan upated with lipase
- Section 8.1.3: updated with the list of adverse events of special interest
- Section 13: update to the list of references
- Appendix 14.1: table title for prohibited concomitant medications requiring caution has been updated with a notation for LDK378, deletion of CYP2C8 substrates and paclitaxel, and updated footnotes for clarification
- Appendix Table 14-2: list of medications to be used with caution updated with deletion of CYP2B6 and CYP2C8 substrates, clarithromycin and telithromycin
- 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. The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Updates to the safety data in the associated Informed Consent Form (ICF) to match the Investigator's Brochure Edition 7 (released on 12 Jun 2014) have been performed separately to this protocol on 15 Sep 2014.

[redacted]

Summary of previous amendments

Amendment 2

Amendment rationale

As of the release date of this amendment, 57 patients have been screened to the study. 45 patients have been treated.

This amendment has been implemented to address the availability of new safety data as represented in the latest Investigator Brochure, to amend the eligible study population, and to clarify sections of the protocol where additional guidance was required:

- Addition a secondary endpoint of overall intracranial response rate (OIRR) due to the interest in LDK378 activity in the brain
- Allowing pre-screening during prior chemotherapy treatment and prior to progression of disease
- Allowing the enrolment of chemotherapy-naive patients to target the ALK-inhibitors-naive population regardless of previous chemotherapy
- Update of safety data in the protocol and associated Informed Consent Form (ICF) to match the Investigator Brochure Edition 4 (release on 28 June 2013).
- Change in definition of duration of response (DOR) in response to health authority feedback and based on the advanced cancer under study and it being difficult to ascertain whether a death is due to the underlying cancer

In addition, editorial changes and text corrections were made for clarification, where required.

This amendment will result in a change to the study population. There is no anticipated extension in the duration or release of results of the study.

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 were changed:

- Sections 1.2.1.2.1, 1.2.1.2.2 and 2.1: clinical safety and efficacy data updated to reflect data most recently available from ongoing studies
- Section 1.2.1.2.4: updated with most recent data from clinical pharmacology studies
- Sections 1, 5 and 6: Information available on pneumonitis cases reported during LDK378 treatment to date have been summarized, an exclusion criteria for patients with pneumonitis added, and dose modification criteria added for patients who experience pneumonitis during the course of the study.
- Sections 2.2, 4.1 and 5: study population changed to allow patients who are chemotherapy naïve to enter the trial.
- Section 3: Changed the definition of duration of response (DOR) from ‘time from first documented response (PR or CR) to the date of first documented disease progression or

[redacted]

death due to underlying cancer' to 'time from first documented response (PR or CR) to the date of first documented disease progression or death due to any cause'.

- Sections 3 and 10: Secondary endpoint of overall intracranial response rate (OIRR) added
- [redacted]
- Section 5.2: inclusion criteria for potassium, magnesium, phosphorus and total calcium changed from requirement to be ≥ LLN to within normal range.
- Section 5.3: exclusion criteria updated to specifically disallow patients with uncontrolled diabetes mellitus from entry to the trial.
- Section 6.1.1: guidance on dosing with LDK378 in relation to food intake has been updated to reflect latest data on clinical pharmacology.
- [redacted]
- Section 6.2.3: added guidance that once the dose of LDK378 has been reduced due to toxicity, it should not be re-escalated.
- Section 7.2.1.1: clarification that all imaging assessments performed in the 6 weeks leading up to first dose may be counted as baseline assessments.
- Editorial and typographical changes through 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.

[redacted]

Amendment 1

Amendment rationale

As of the release date of this amendment, 5 patients have been screened to the study. 3 patients have been treated.

This amendment has been implemented to address six main items with the original protocol released for the study, reflecting the availability of new toxicity data, addressing requests from health authorities, and clarifying sections of the protocol where additional guidance was required:

- To add an ECG assessment for all patients 6 hours after first dose
- To provide general guidance on dose modification
- To provide guidance on dose modification in response to QTc prolongation
- To provide guidance for treatment of hypophosphatemia
- To clarify tumor sample collection requirements

In addition, editorial changes and text corrections were made for clarification, where required.

This amendment will result in no change to the study population. There is no anticipated extension in the duration or release of results of the study.

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 of the protocol were changed:

In Section 1.1.3, information on ALK positive NSCLC data and regulatory approvals status have been updated.

[redacted]

In Section 1.2.1.1.4, based on emerging safety data made available, LDK378 may have an effect on the QT interval, hence the last sentence regarding "…suggesting that there is no clinical risk for QTc prolongation" was removed. Additionally data regarding phototoxicity was added.

In Section 1.2.1.2.1, information on hypophosphatemia and QT data was added.

[redacted]

In Section 4.1, naming of the FDA-approved FISH test has been updated and aligned throughout the entire document.

[redacted]

In Section 4.2, sub-sections have been added to bring clarity to the tumor samples requirements. In addition, the new biopsy sampling timing has been corrected to 'time of progression' instead of 'end of treatment'.

In Section 4.3, sentence has been added to confirm Novartis will commit to their reporting obligations, for patients receiving LDK378 on a separate protocol.

In Section 5.2, in inclusion criteria no 1, 3 and 4, locally advanced or metastatic were replaced by Stage IIIb or IV, for clarity purpose. In inclusion criteria no 3, it has been clarified that patients must have progressed during or after the last chemotherapy regimen received prior to the first dose of LDK378. In addition, in inclusion no 4, cytotoxic chemotherapy definition has been slightly corrected to include duration of 21 days. In inclusion no 7, abbreviation for Alanine transaminase has been corrected to ALT. An additional inclusion criterion was added for laboratory parameters for magnesium, potassium, phosphorus and calcium, and the inclusion criteria for creatinine clearance was changed from > 50 mL/min to > 30 mL min to allow inclusion of patients with moderate renal impairment . Renal clearance of LDK378 is less than 1% in rats and monkeys and in preliminary data from a human ADME study. In addition, in the CLDK378X2101 phase I study of over 200 patients, no significant renal toxicities were reported, and in the small subgroup of patients with mild renal impairment no excess toxicities were noted.

In Section 5.3, exclusion criteria no 5, additional information regarding QTcF calculation has been added as it was missing in the original document. In addition, medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes has been added as a sub-bullet in exclusion no 10. Tumor-associated symptoms have been clarified in exclusion no 13.

In Section 6.1.1, meal instructions have been updated to reflect the updated data from food effect study.

In Section 6.2.1, general guidelines for dose modifications have been added as per Health Authorities request.

In Section 6.2.2, treatment interruption guidance for reasons other than toxicity has been added as it was missing from the original document, and treatment interruption guidance for toxicity has been updated to be aligned with the treatment schedule of 28 days cycles.

In Table 6-3 and Table 6-4, 'total' was added for bilirubin as it was missing from the original document. In addition, guidance on dose modification in response to QTc prolongation was added as it was missing from the original document. Table 6-4 was moved to the end of section 6.2.4.1, to be consistent with the text.

In Section 6.2.4.2, 'total' was added for bilirubin as it was missing from the original document.

In Section 6.2.4.6, guidance for the treatment hypophosphatemia was added as it was missing in the text.

In Section 6.3.1, clarification has been made when corticosteroids are use when used for CNS related symptoms.

In Section 6.3.1.5, the use of gastric protection agents has been further clarified.

[redacted]

In Section 6.3.2, a sub-section has been added regarding medications that may prolong the QT interval or have a known risk of inducing Torsades de Pointes.

In Section 6.4.1, the use of the IRT system has been clarified at the screening visit. Information has been as well added in regard to the use of the IRT system when the patient is enrolled.

In Section 7.1, Table 7-1 was corrected to reflect the current assessments performed as some were not captured in the original document.

In Section 7.1.3.2, criteria for patient withdrawal have been clarified to reflect Health Authorities' request.

In Section 7.2.1, it has been specified that Contrast-enhanced CT needs to be performed with IV contrast, and that upper abdomen needs to be evaluated. In addition, it is now allowed to provide as protocol required baseline scans, the scans that were already completed during the regular work-up of the patient within 6 weeks prior to start of treatment and before signing the main study ICF.

In Section 7.2.2.5, laboratory evaluations have been re-worded to make the distinction between central/local assessments for out-of-schedule assessments and out-of-range parameters.

In Section 7.2.2.6, an ECG assessment has been added for all patients 6 hours after first dose. Further changes have been done to bring clarity to the section.

[redacted]

In Section 8.4, clarification has been made that patients who become pregnant during the trial will be withdrawn from study as requested by Health Authorities, and that pregnancy should be followed until 3 months following delivery.

In Section 10, minor changes have been done throughout the section to bring clarity and to align with LDK378 program analysis standards. The definition of the per-protocol set was changed to include patients who have a follow-up tumor assessment > 7 weeks (rather than 8 weeks) after starting treatment to take into consideration the +/-1 week window associated with tumor assessments; the definition of safety data set was changed to align with the LDK378 program standard (now includes all patients who receive at least one dose of study drug).

In Section 14 Appendix I, Table 14-1 references have been updated. Table 14-2 has been updated with a list of proton pump inhibitors, as it was missing in the original document. In addition a new table showing the list of prohibited QT prolonging drugs has been added as per Health Authorities request.

Editorial changes were performed throughout the document.

[redacted]

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.

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). This year, approximately 160,000 deaths are expected in the US (Siegel et al 2012) and 262,000 in the European Union (Malvezzi et al 2012).

The World Health Organization (WHO) divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: non-small cell lung cancer (NSCLC) and small cell lung cancer. NSCLC accounts for more than 85% of all lung cancer cases, and it includes 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 frequently occurring cell type in nonsmokers (NCCN Guidelines® v3.2012).

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.

One reason for the high mortality rate of lung cancer is the advanced stage at diagnosis; 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 and they are not candidates for surgery.

As summarized in the current NCCN Guidelines for NSCLC, data show that platinum-based combination therapy is superior to best supportive care for patients with advanced, incurable disease. Platinum-doublets (cisplatin or carboplatin in combination with other chemotherapy agents, with or without bevacizumab) is the standard in first line treatment of locally advanced or metastatic NSCLC, unless a patient has a known “druggable” mutation, and is a candidate for a targeted therapy (as discussed below). Docetaxel, pemetrexed, erlotinib, or platinum doublet (with or without bevacizumab) are recommended as second-line chemotherapy regimens for patients who have experienced disease progression during or after first-line therapy. The reported response rates to second-line chemotherapy have generally been less than 10%. 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 overall survival rate of only 15% (Nguyen et al 2012).

1.1.2 Targeted therapies in NSCLC

During the last few years, improved knowledge of NSCLC biology led to the identification of molecular events crucial for malignant transformation and cancer cell survival. These aberrant molecular events are critical oncogenic drivers and, therefore, represent potential therapeutic targets (Gettinger et al 2011). As a result, new targeted treatment options are evolving.

[redacted]

Bevacizumab, a monoclonal antibody directed against vascular endothelial growth factor-A (VEGF-A), and erlotinib and gefitinib, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), have been approved for the treatment of NSCLC (Gettinger et al 2011). In particular, the case of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) represents a new paradigm in the treatment of NSCLC. Mutations in EGFR are found in 10–26% of NSCLC patients and are associated with response to oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, gefitinib and erlotinib, and the monoclonal antibody to EGFR, cetuximab (National Cancer Institute PDQ®).

Multiple large randomized clinical trials have demonstrated that patients harboring activating EGFR mutations benefit more from EGFR TKIs than from standard chemotherapy in terms of response rate, progression free survival, toxicity profile and quality of life (reviewed in NCCN Guidelines® v3.2012). 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 positive NSCLC

The discovery of anaplastic lymphoma kinase (ALK) rearrangement in NSCLC in 2007 (Soda et al 2007) represents another important milestone in the era of molecular targeted therapy in NSCLC.

ALK was first identified as a chromosome translocation-produced protein fusion in the majority of anaplastic large cell lymphomas (ALCL). When fused to other proteins, ALK becomes constitutively active, leading to increased catalytic kinase function, signal-transduction activity, and oncogenic function. Expression of EML4-ALK - a new fusion protein between ALK and the echinoderm microtubule-associated protein-like 4 (EML4) gene- in transgenic mice has been shown to induce tumor formation, suggesting the therapeutic potential of targeting the EML4-ALK fusion protein in NSCLC (Soda et al 2007). The frequency of EML4-ALK rearrangement in patients with NSCLC is relatively low; it is present in approximately 2-8% of tumors tested (Scagliotti 2012; Takeuchi 2009; Soda 2007). However, considering the high incidence of lung cancer, this small percentage translates into about 10,000 patients in the United States alone (Kwak et al 2010).

These patients are similar to those with EGFR mutations (i.e., adenocarcinoma, nonsmokers or light smokers) except they are often younger. In addition, ALK rearrangements are found in patients with adenocarcinoma but are usually not been found in squamous cell or large cell carcinoma (Shaw et al 2009). 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. 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, an orally available small-molecule inhibitor of ALK and MET tyrosine kinases, has been rapidly and successfully developed in patients with advanced NSCLC who have EML4-ALK rearrangements and have progressed on previous therapy. Crizotinib was associated with clinically meaningful response rates of 50% and 61%, respectively, in two single-arm trials in 255 patients with locally advanced or metastatic ALK-positive NSCLC

(Ou 2011). 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 of 9.78 and 11.22 months, respectively, in each of the studies. Based on these data, crizotinib (Xalkori®) received accelerated approval by the US Food and Drug Administration in August 2011 for the treatment of ALK-rearranged NSCLC. It has also been approved in South Korea, Switzerland, Japan and Canada and received conditional marketing authorization in the EU on 23-Oct-2012 for the treatment of adult patients with previously treated ALK-positive advanced NSCLC. Retrospective comparison of these data for the subset of patients treated in the second-line to ALK-positive positive patients who were treated with other second-line chemotherapy suggested an overall survival advantage (median OS: not reached versus 6 months, HR=0.36, p=0.004) (Shaw et al 2011).

While crizotinib has substantial activity in patients with ALK rearranged NSCLC, these cancers invariably progress, typically within 1 year, because of the development of resistance to crizotinib (Ou 2011).

CH5424802 is another ALK inhibitor in clinical development. As opposed to crizotinib, CH5424802 is a specific ALK inhibitor. In a phase 1 trial in patients with ALK positive NSCLC who have failed prior chemotherapy, but were crizotinib naïve, a response rate of 85% was reported in 20 patients with measurable lesions (Kiura et al 2012). These data highlight the fact that NSCLC harboring ALK rearrangements are responsive to specific ALK inhibitors, with a response rate higher to that expected with chemotherapy and at least comparable to the response rate obtained after crizotinib. In addition, these data also reaffirm that ALK rearrangement represent the key oncogenic driver in these tumors and that specific ALK inhibition provides substantial anti-tumor activity.

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

In addition, LDK378 shows potent antitumor activity in crizotinib-resistant animal models.

These features support the hypothesis that LDK378 could be active in NSCLC patients whose disease has progressed on crizotinib.

1.2.1.1 Non-clinical experience

1.2.1.1.1 Pharmacology

[redacted]

[redacted]

1.2.1.1.2 Antitumor activity in xenograft models

[redacted]

1.2.1.1.3 Non-clinical pharmacokinetics (PKs) and metabolism

[redacted]

[redacted]

1.2.1.1.4 Safety pharmacology and toxicology

[redacted]

[redacted]

[redacted]

1.2.1.2 Clinical experience

1.2.1.2.1 Clinical safety and tolerability

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

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

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

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

[redacted]

	LDK378 750 mg N=255	
	All Grades	Grade 3/4
Preferred term	n (%)	n (%)
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. AEs leading to study drug discontinuations occurred in 10.2% of patients treated with LDK378 at the 750 mg dose. The most frequent AEs leading to study drug discontinuations were decreased appetite, pneumonia, ALP increased, pneumonitis, and respiratory failure.

Serious adverse events (SAEs) reported in 2% or more of the 255 patients treated at the recommended dose of 750 mg were convulsion, pneumonia, interstitial lung disease (ILD)/pneumonitis, dyspnea, hyperglycemia, and nausea. Fatal adverse reactions occurred in 5% of patients, consisting of: pneumonia (4 patients), respiratory failure, ILD/pneumonitis, pneumothorax, gastric hemorrhage, general physical health deterioration, pulmonary tuberculosis, cardiac tamponade, and sepsis (1 patient each). Adverse events of special interest (AESIs) to be monitored for LDK378 have also been identified and include: hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations). For additional details, refer to [Investigator's Brochure].

1.2.1.2.2 Clinical efficacy

LDK378 has demonstrated potent antitumor activity in patients with advanced, ALK-rearranged NSCLC (Shaw et al 2013). Among 114 response-evaluable patients with at least 18 weeks of follow-up prior to 28 Feb, 2013, or who discontinued study earlier, and were treated with LDK378 doses of 400 mg qd or higher, 66 (58%) patients have responded (Table 1-2). In addition, the response rate to LDK378 is similar regardless of prior ALK inhibitor therapy. In patients with NSCLC treated at ≥400 mg qd, who had previously received crizotinib, the response rate was 57%, and in those who had not previously received crizotinib it was 60%. Post-baseline tumor measurements are available for 104 of the 114 response evaluable patients. A waterfall plot displaying the maximum decrease from baseline in the sum of the longest tumor diameters (Figure 1-1) shows that the large majority of patients treated with LDK378 had a reduction in tumor burden. The median duration of response in

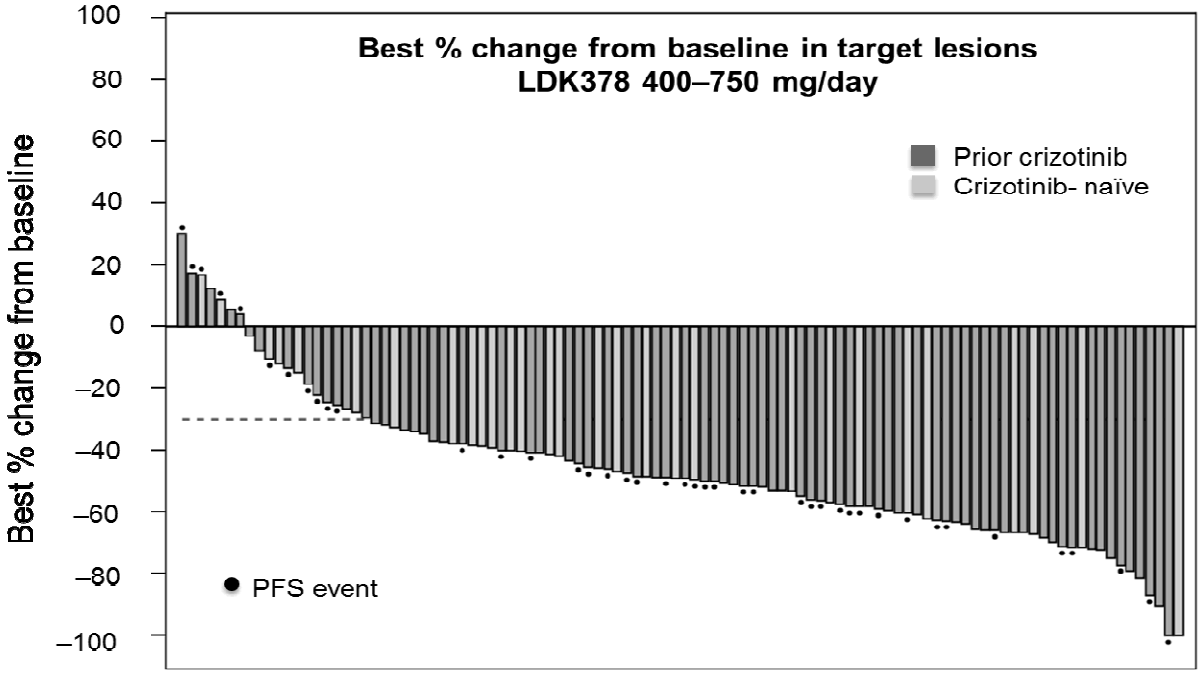
[redacted]

patients who responded and were treated at ≥400 mg qd was 8.2 months (95% CI: 6.9, not estimable), and 71% had a duration of response of 6 months or longer.

Table 1-2 Study CLDK378X2101 Response Rate

Response rate (RECIST v1.0)	N	CR n (%)	CR + PR n (%)
All NSCLC, ≥400 mg/d	114	1 (1)	66 (58)
NSCLC, at 750 mg	78	0	47 (60)
ORR by prior crizotinib treatment			
NSCLC prior crizotinib, ≥400 mg/d	79	1 (1)	45 (57)
NSCLC prior crizotinib, 750 mg/d	49	0	29 (59)
NSCLC crizotinib naive, ≥400 mg/d	35	0	21 (60)
NSCLC crizotinib naïve 750 mg/d	29	0	18 (62)

Figure 1-1 Waterfall plot of reduction in sum of longest tumor diameters



The available data from the ongoing phase I study indicate that LDK378 has substantial antitumor activity in patients with ALK-rearranged NSCLC whose disease has failed crizotinib therapy or who are naïve to crizotinib therapy.

1.2.1.2.3 Clinical pharmacodynamics

Data are not available from the ongoing clinical study.

[redacted]

1.2.1.2.4 Clinical pharmacokinetics

[redacted]

[redacted]

1.3 Risks and benefits

Overall benefit-risk

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

Efficacy

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

The efficacy of LDK378 seen in Study [CLDK378X2101] is highly encouraging in heavily pretreated patients with advanced disease, high tumor burden (including a high proportion of brain metastases at baseline), limited available therapeutic options, and dismal prognoses

[redacted]

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

[redacted]

Safety

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

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

Risk management during study conduct

In order to manage the risks associated with LDK378 treatment, specific dose modifications and stopping rules during study conduct are described in the protocol. For patients who do not tolerate the initial protocol-specified dose, dose adjustments are provided in order to allow the patients to continue the study treatment (Section 6.2 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.

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

[redacted]

Detailed information on allowed and prohibited concomitant medications is provided in Section 6.3. *In vitro* drug metabolism studies show that the metabolism of LDK378 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 LDK378. Prohibited medications should be discontinued at least 1 week prior to the start of treatment with LDK378 (see exclusion criteria #8).

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: cases of hepatotoxicity occurred in less than 1% of patients treated with LDK378 in clinical studies. Increases to grade 3 or 4 ALT elevations were observed in 25% of patients receiving LDK378. Concurrent elevations in ALT >3xULN and total bilirubin >2xULN, with normal alkaline phosphatase, occurred in less than 1% of patients in clinical studies. The majority of cases were manageable with dose interruption and/or dose reduction. Few events required discontinuation of LDK378. Patients will be closely monitored by regular laboratory testing and related signs and symptoms. Risk to patients will also be minimized by restricting study enrollment to subjects with laboratory values for AST, ALT, ALP and bilirubin below certain thresholds (see inclusion criteria #7).
- Interstitial lung disease/pneumonitis: severe, life-threatening, or fatal interstitial lung disease (ILD)/pneumonitis have been observed in patients treated with LDK378 in clinical studies. Most cases improved or resolved with interruption of LDK378. Patients will be monitored for symptoms such as shortness of breath, cough or fever. Risk to patients will be minimized by excluding from study enrollment any patient with a history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention) (see exclusion criteria #19).
- QT interval prolongation: QTc prolongation has been observed in clinical studies in patients treated with LDK378, which may lead to an increased risk for ventricular tachyarrhythmias (e.g., Torsade de pointes) or sudden death. A pharmacokinetic analysis suggested that LDK378 causes concentration-dependent increases in QTc. Repeated ECG tracings will be performed throughout the study to closely monitor cardiovascular safety. Risk to patients will also be minimized by excluding from study enrollment those patients with clinically significant, uncontrolled heart disease and/or a recent cardiac event (within 6 months), including a corrected QT (QTcF) > 470 ms using Fridericia's correction on the screening ECG (see exclusion criteria #5).
- Bradycardia: asymptomatic cases of bradycardia have been observed in patients treated with LDK378 in clinical studies. Repeated ECG tracings will be performed throughout the study to closely monitor cardiovascular safety. Risk will also be minimized by monitoring concomitant use of other agents known to cause bradycardia (e.g., beta-blockers, non-dihydropyridine calcium channel blockers, clonidine, and digoxin) to the extent possible. Heart rate and blood pressure will also be monitored regularly during the study.
- Hyperglycemia: events of hyperglycemia (all grades) have been reported in less than 10% of patients treated with LDK378 in clinical studies; 5% of patients reported a grade 3/4 event. The risk of hyperglycemia was higher in patients with diabetes mellitus and/or

[redacted]

concurrent steroid use. Patients will be closely monitored throughout the study for any signs and symptoms related to elevated blood glucose levels.

- Gastrointestinal toxicity: diarrhea, nausea, and vomiting have been very commonly reported; 12.2% of patients reported a grade 3/4 event of diarrhea, nausea, or vomiting. Risk to patients will be minimized during the study by closely monitoring symptoms and managing patients using standards of care, including anti-diarrheals, anti-emetics, or fluid replacement, as indicated.
- Pancreatitis (including lipase and amylase elevations): in most cases, pancreatic enzyme elevations have been mild to moderate, and have typically reversed with interruption of LDK378. Few patients have experienced pancreatitis with severe upper abdominal pain. Patients will be monitored closely for any related signs and symptoms.

Conclusion

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

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

2 Rationale

2.1 Study rationale and purpose

ALK rearrangement is a relatively rare event in NSCLC with a frequency of 2-8% (Scagliotti 2012; Takeuchi 2009; Soda 2007). This rearrangement results in aberrant ALK activation. ALK fusion proteins possess potent oncogenic activity both *in vitro* and *in vivo*. This activity can be effectively blocked by small-molecule inhibitors that target ALK.

The purpose of this phase II study is to evaluate the antitumor activity and safety profile of the novel ALK inhibitor LDK378 when used as a single agent in patients with ALK-rearranged locally advanced or metastatic NSCLC who have not been pretreated with crizotinib.

[redacted]

[redacted]

[redacted]

2.2 Rationale for the study design

This is a prospective, multi-center, open-label, single arm, phase II study with two-stage design to evaluate the efficacy and safety of single-agent LDK378 in patients with ALK-rearranged NSCLC not previously treated with crizotinib. Patients may have received up to three prior lines of cytotoxic chemotherapy. In such cases, patients must have progressed during or after the chemotherapy regimen received prior to the first dose of LDK378. Patients will also be eligible for the study if they have never been treated with chemotherapy for their NSCLC.

The primary objective is to demonstrate the antitumor activity of LDK378 in this population. The primary measure of antitumor activity is the ORR according to RECIST 1.1 and will be estimated based on investigator assessment. In addition, there will be an independent radiological review by a blinded independent review committee (BIRC). Response rate is an appropriate primary endpoint that can be adequately assessed in the context of this single arm phase II trial. A high ORR may predict clinical benefit in this rare population of patients with ALK-rearranged NSCLC. Indeed, crizotinib was approved by certain Health Authorities in this indication based on data from two single arm trials using ORR based on investigator assessment as primary endpoint. Data on ORR will be supplemented with data on duration of response (DOR) and time to response (TTR).

Based on the data available with LDK378 in crizotinib naïve patients in the ongoing phase I study at the time of the study design, the present study will use a two-stage design. The Data Monitoring Committee will evaluate the ORR data from Stage 1 and, based on pre-specified response criteria (see Section 10.7), will make the recommendation whether to proceed to Stage 2 or stop the trial.

[redacted]

The study will also assess progression-free survival (PFS), overall survival (OS) and impact on Patient Reported Outcomes (PROs) with LDK378 treatment. These endpoints are considered to be important supportive endpoints to better assess the potential clinical benefit of LDK378. In addition an evaluation of the activity of LDK378 on brain metastases will be included as a secondary objective in this study.

Safety will be monitored throughout the course of the study.

2.3 Rationale for dose and regimen selection

[redacted]

3 Objectives and endpoints

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

[redacted]

Table 3-1 Objectives and related endpoints

Objective	Endpoint	Analysis
Primary		**Refer to Section 10.4.**
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 or partial response (CR+PR) as assessed by investigator	
Key secondary		**Refer to Section 10.5.1.**
To evaluate response related endpoints as assessed by investigator and Blinded Independent Review Committee (BIRC): 1. Duration of response (DOR) 2. Disease control rate (DCR) 3. Time to Response (TTR) 4. Overall intracranial response rate (OIRR) And to assess: 5. ORR by BIRC assessment	The following endpoints will be evaluated by investigator assessment and BIRC 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 death due to any cause 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 And: 5. ORR (CR+PR) per RECIST 1.1 as assessed by BIRC	
Other secondary		**Refer to Section 10.5.2.**
1. To evaluate the safety profile of LDK378 2. To evaluate progression-free survival (PFS) 3. To evaluate overall survival (OS)	1. Adverse events and laboratory abnormalities 2. PFS, defined as time from first dose of LDK378 to progression or death due to any cause, as assessed by BIRC and investigator assessment 3. OS, defined as time from first dose of LDK378 to death due to any cause	

[redacted]

Objective	Endpoint	Analysis
[redacted]		

4 Study design

4.1 Description of study design

This is a single-arm, open-label, two-stage, multicenter, phase II study in which the efficacy and safety of LDK378 will be evaluated in patients with locally advanced or metastatic NSCLC harboring a confirmed ALK rearrangement, defined as 15% or more positive lung tumor cells as assessed by the FDA-approved FISH test (Abbott Molecular Inc.) using Vysis break-apart probes.

Overview of the study design

Patients will be pre-screened to test for ALK positivity. The test to confirm ALK rearrangement must be performed either using archival tissue or, preferably, using a new biopsy prior to study entry according to the above criteria, i.e. with the FDA-approved Vysis ALK break-apart FISH assay. The test will be performed at a Novartis designated central laboratory.

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

Patients must not have received prior crizotinib. Patients may have been treated with cytotoxic chemotherapy (up to 3 lines). In such cases, patients must have progressed during or after the last chemotherapy regimen received prior to the first dose of LDK378. Patients will also be eligible for the study if they have never been treated with chemotherapy for their NSCLC.

The study will use a Simon's optimal two-stage design. Stage 1 will consist of 43 patients and their data up to 6 cycles of treatment unless a patient has discontinued treatment earlier or a confirmed response to treatment has been observed prior to completing 6 cycles. The trial will be stopped at Stage 1 for futility if 16 or fewer responses are observed. If at the time that the last patient is enrolled to Stage 1 a minimum of 17 responses have not yet been observed, accrual may be temporarily suspended during the analysis of Stage 1. The Data Monitoring Committee will periodically review response data and will make the appropriate recommendation regarding transition into Stage 2 or stopping enrollment (see Section 8.6).

Stage 2 will include an additional 62 patients. The primary analysis will occur when all 105 patients have completed 6 cycles of treatment or discontinued treatment earlier. Patients will follow the study design shown in Figure 4-1 and have study assessments as described in Section 7.

The treatment period begins on Day 1 of Cycle 1. All patients will be treated with LDK378, administered orally, at a starting dose of 750 mg. A total of approximately 105 patients will be enrolled in the study. Patients will take LDK378 once daily, at approximately the same time each day. [redacted] 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. If the patient experiences RECIST-defined progressive disease (PD) on LDK378 as

[redacted]

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.

Assessments of tumor response and progression will be performed every 8 weeks (i.e. every 2 cycles), starting from the first day of treatment with LDK378. This schedule of tumor assessment every 8 weeks must continue regardless of dose interruptions. Tumor assessment should continue until:

- For patients who experience PD as assessed by the investigator, tumor assessments should continue every 8 weeks until LDK378 is permanently discontinued (i.e. if the patient continues treatment with LDK378 after PD, tumor assessments should continue until LDK378 is permanently discontinued).
- For patients who discontinue treatment in the absence of PD, tumor assessments should continue every 8 weeks from the EOT visit until PD is assessed by the investigator.

Tumor evaluations will always cease if the patient withdraws consent (unless the patient agrees to continue efficacy assessments in absence of dosing with LDK378, see Section 7.1.4.1), or dies.

All tumor imaging assessments will be submitted for independent radiological assessment of response by a Blinded Independent Review Committee (BIRC).

Clinical and laboratory assessments will be performed as described in Section 7.

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 end of tumor assessments, the Study Phase Completion Disposition eCRF must be completed. Patients will be contacted every 3 months to obtain information pertaining to survival status until death, loss to follow-up, withdrawal of consent to survival follow-up, or the end of the study (as defined in Section 4.3). Patients do not need to visit the clinic during the survival follow-up.

4.2 Tumor sample requirements

There are two parts to the tumor sample requirements of the trial:

- In order to test ALK status at the molecular pre-screening stage, all patients must have a tumor tissue sample available, preferably as a newly obtained tumor biopsy or, if a new biopsy is not obtainable or the patient does not agree, an archival tumor biopsy collected either at the time of NSCLC diagnosis or any time since. All available tumor tissue, whether new biopsy or archival sample, should be sent to the central laboratory at pre-screening.
- If a new biopsy was not collected at molecular pre-screening, patients must be asked at screening if they are willing to provide a new tumor tissue biopsy (although participation is optional). Consent for this sample must be obtained via the additional optional Informed Consent Form (ICF). [redacted]

[redacted]

[redacted]

4.2.1 Archival tissue

Acceptable archival tumor tissue may consist of a formalin fixed paraffin embedded (FFPE) NSCLC tumor block or at least 7, preferably 15, slides 5 µm thick. If a tumor block is provided, the remaining tissue will be returned to the site upon request. Note: Cytology samples from pleural fluid can not be used for testing ALK status.

4.2.2 New biopsies

Preferably, a new tumor biopsy should be obtained at pre-screening if the patient agrees on the molecular pre-screening consent form.

[redacted]

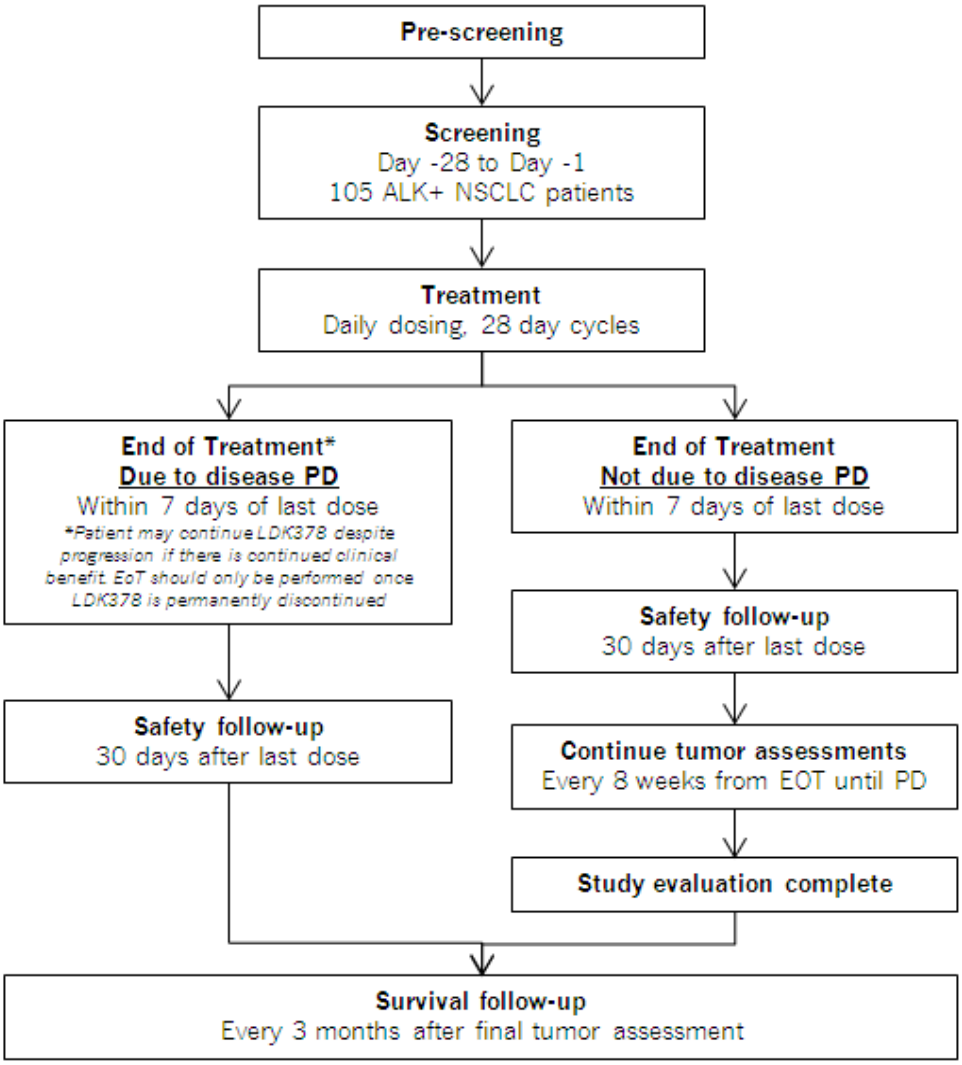
4.2.3 Tumor samples analyses

Any tumor tissue sample obtained will be utilized for two purposes:

- Determination of ALK status using the FDA-approved Vysis ALK break-apart FISH assay (Abbott Molecular Inc.): the test to assess ALK rearrangement will be performed by a Novartis designated central laboratory. The test will be performed on the new tumor biopsy obtained at pre-screening if the patient has consented to the biopsy. If a new biopsy is not available, the test to determine ALK status will be performed using the archival lung tumor tissue. Note: Cytology samples from pleural fluid can not be used for testing ALK status.
- [redacted]

[redacted]

Figure 4-1 Study design



4.3 Definition of end of the study

There will be no interim analysis of efficacy. The primary analysis will occur once all patients have completed at least 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 will continue as per the schedule of assessments.

Following the cut-off date for the analysis reported in the primary CSR, the study will remain open. Ongoing patients will continue to receive study treatment and be followed as per the schedule of assessments, as long as patients derive benefit from LDK378. The end of study defined as the earliest occurrence of one of the following:

- At least 75% of patients have died or all patients discontinued from the study.
- Other clinical studies (e.g. roll-over protocol or other) or patient support programs become available that can continue to provide LDK378 in this patient population and all patients ongoing are eligible to be transferred to them.
- At the end of the study, every effort will be made to continue provision of study treatment outside this study through an alternative setting to patients who in the opinion of the Investigator are still deriving clinical benefit.

The final analysis will occur at the end of the study. All available data from all patients up to this cut-off date will be analyzed and summarized in a final CSR.

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 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 crizotinib-naïve adult patients with ALK-rearranged (as determined by the FDA-approved Vysis ALK break-apart FISH assay) locally advanced or metastatic NSCLC who are either chemotherapy-naïve or who have been previously treated with cytotoxic chemotherapy (up to 3 lines).

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

See Section 7.1.1 for details on pre-screening procedures.

Patients enrolled in this study are not permitted to participate in 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.

[redacted]

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 stage IIIB or IV NSCLC that carries an ALK rearrangement defined as 15% or more positive tumor cells as assessed by the FDA-approved FISH test (Abbott Molecular Inc.) using Vysis break-apart probes. Patients will be pre-screened to test for ALK positivity. The test to confirm ALK rearrangement must be performed either using archival tissue or, preferably, using a new biopsy prior to the first dose of LDK378 according to the above criteria, i.e. with the FDA-approved Vysis ALK break-apart FISH assay. The test will be performed at a Novartis designated central laboratory.
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.
4. Patients must be chemotherapy-naïve or have received up to 3 lines of prior cytotoxic chemotherapy to treat their stage IIIB or IV NSCLC. If patients received chemotherapy, such patients must have progressed during or after the last chemotherapy regimen received prior to the first dose of LDK378.
   - Prior erlotinib or gefitinib will not count as a line of cytotoxic chemotherapy (i.e. patients may have received prior treatment with these drugs)
   - (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 or metastatic (stage IIIB or IV) disease is defined as an anticancer regimen that contains at least 1 cytotoxic chemotherapy agent and is given for 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.
5. Patients must have a tumor tissue sample available, preferably being a new biopsy but otherwise being an archival sample collected either at the time of diagnosis of NSCLC or any time since, for assessing ALK rearrangements using the FDA-approved Vysis ALK break-apart FISH assay (see Section 4.2).
6. 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.
7. Patients must meet the following laboratory values at the screening visit:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
   - Platelets ≥ 75 x 10^9/L
   - Hemoglobin (Hgb) > 8 g/dL
   - Calculated creatinine clearance (using Cockcroft-Gault formula) > 30 mL/min

[redacted]

- Total bilirubin < 1.5 x ULN (Upper limit of normal), 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) < 3 x ULN, except for patients with liver metastasis, who are only included if AST < 5 x ULN
- Alanine transaminase (ALT) < 3 x ULN, except for patients with liver metastasis, who are only included if ALT < 5 x ULN
- Patients must have the following laboratory values within the laboratory normal limits or corrected to within normal limits with supplements during screening:
  - Potassium
  - Magnesium
  - Phosphorus
  - Total calcium (corrected for serum albumin)

8. Life expectancy ≥ 12 weeks.
9. World Health Organization (WHO) performance status 0-2.
10. 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.
11. 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.
12. 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. Prior treatment with crizotinib, or any other ALK inhibitor investigational agent, for NSCLC
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. Clinically significant, uncontrolled heart disease, 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)

[redacted]

- Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mm Hg and/or Diastolic Blood Pressure (DBP) ≥ 100 mm Hg, with or without anti-hypertensive 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 Fridericia correction (QTcF) on the screening ECG (as mean of triplicate ECG)

6. 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 patients who have not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment is allowed.
7. 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.
8. 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:
   - Strong inhibitors or strong inducers of CYP3A4/5 (Appendix I)
   - Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5, CYP2C8 and/or CYP2C9 (Appendix I)
   - Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes (Appendix I)
9. 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).
10. Patients who are currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants.
11. 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.
12. Patients receiving treatment with any enzyme-inducing anticonvulsant (Appendix I) 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.
13. Investigational agents within 4 weeks or ≤ 10 x half-life of the agent (whichever is longer) before first dose of study treatment.

[redacted]

14. 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.
15. 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 30 days after stopping treatment. **Highly effective** contraception is defined as any of:
    1. Total abstinence: when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].
    2. 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.
    3. Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female subjects on the study the vasectomized male partner should be the sole partner for that patient].
    4. 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.
        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.
16. 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.
17. Other severe, acute, or chronic medical or psychiatric conditions including uncontrolled diabetes mellitus 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.
18. Patients with known hypersensitivity to any excipients of LDK378 (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate).
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).

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 patient supply, packaged in bottles. LDK378 will be dosed on a flat scale of 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. A complete cycle of treatment is defined as 28 days of once daily treatment of LDK378. The investigator must instruct the patient to take the study drug exactly as prescribed.

[redacted]

- 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.

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)

[redacted]

[redacted]

6.1.2 Guidelines for continuation of treatment

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

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 as assessed by the investigator. Patients who have RECIST-defined PD as assessed by the investigator, 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 and efficacy assessments as per the schedule of assessments.
- Unacceptable toxicity that precludes further treatment
- Start of a new anti-cancer therapy
- And/or treatment is discontinued at the discretion of the investigator or patient or the patient is lost to follow-up.

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

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

[redacted]

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.

LDK378 dose modification guidelines are described in Section 6.2.3 and Table 6-3. 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).

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 or grade 3 treatment-related toxicities, dosing should be interrupted until at least resolution to grade 1 followed by dose reduction. For any grade 4 toxicity, patients should interrupt study treatment until resolution to at least grade 1, followed by either dose reduction or treatment discontinuation. Treatment with the study drug may subsequently be continued at a reduced dose level if in the opinion of the investigator the patient continues to experience clinical benefit and after discussion with the sponsor.

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 will 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 6.2.3, provided this toxicity resolved to ≤ CTCAE grade 1.If the treatment with LDK378 is withheld due to toxicity, scheduled visits and all assessments (including tumor assessments) will continue to be performed (with the exception of the dosing of the withheld study drug), as described in Table 7-1.

If the treatment with LDK378 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.

If the treatment with LDK378 dosing is withheld for more than 28 consecutive days (counting from the first day when a dose was missed) for reasons other than toxicity, then LDK378 should be permanently discontinued. If dosing was withheld for up to 28 consecutive days for

[redacted]

reasons other than toxicity, then treatment with LDK378 may be resumed at the same dose if the patient is continuing to derive clinical benefit. 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. Detailed guidelines for follow-up of study drug related AEs or abnormal laboratory values must be followed as described in Section 6.2.4.

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 reductions will be allowed. All dose reductions will be in 150 mg decrements per reduction. The patient must be discontinued from treatment with LDK378 if further reduction is necessary.

Once the dose of LDK378 has been reduced due to toxicity, it cannot be re-escalated.

Table 6-2 Dose reduction steps for LDK378

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

*Dose reduction should be based on the worst preceding toxicity as per NCI-CTCAE version 4.03
**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

Dose changes must be recorded on the Dosage Administration Record eCRF.

Dose Modifications for LDK378 as specified in Section 6.2.3.	
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 GGT	
Isolated elevations of any grade	Maintain dose level
Total Bilirubin** (for patients with Gilbert Syndrome these dose modifications apply to changes in direct [conjugated] bilirubin only)	
Grade 1 (> ULN and ≤ 1.5 x ULN)	Maintain dose level with LFTs*** monitored as per protocol
Grade 2 (> 1.5 and ≤ 3.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ 1 dose level

[redacted]

Grade 3 (> 3.0 and ≤ 10.0 x ULN) with ALT or AST ≤ 3.0 x ULN	Omit dose until resolved to ≤ Grade 1, then: If resolved in ≤ 7 days, ↓ 1 dose level If resolved in > 7 days discontinue patient from LDK378
Grade 4 (> 10.0 x ULN)	Permanently discontinue patient from LDK378
AST or ALT	
Grade 1 (> ULN and ≤ 3.0 x ULN)	Maintain dose level with LFTs*** monitored per protocol
Grade 2 (> 3.0 and ≤ 5.0 x ULN) without total bilirubin elevation to > 2.0x ULN	Maintain dose level with LFTs*** monitored per protocol
Grade 3 (> 5.0 and ≤ 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	Omit dose until resolved to ≤ Grade 1 (or to baseline) 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 (or to baseline) then ↓ 1 dose level
AST or ALT and concurrent Total Bilirubin	
AST or ALT > 3.0 x ULN and total bilirubin > 2.0x 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 LDK378 for acute onset of new or progressive unexplained abdominal symptoms, such as severe pain or vomiting; perform diagnostic procedures (e.g., abdominal CT scan or ultrasound) to exclude pancreatic pathology.	
RENAL	
Serum creatinine	
Grade 1 (>1 and ≤1.5 x baseline; >ULN -1.5 x ULN)	Maintain dose level
Grade 2 (>1.5 and ≤3.0 x baseline; > 1.5 -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 - 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]

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 omit 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
CARDIAC	

[redacted]

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 < 481ms, then ↓ 1 dose level - Assess the quality of the ECG recording and the QT value and repeat if needed Repeat ECG in 24 hours, or less, as clinically indicated; continue monitoring as clinically indicated until 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 [redacted] 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 > 60ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia)	Permanently discontinue patient from LDK378
Bradycardia	
Grade 1 or 2	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥60 bpm Evaluate concomitant medications known to cause bradycardia, and adjust the dose of LDK378
Grade 3 Grade 4 (in patients taking a concomitant medication also known to cause bradycardia or a medication known to cause hypotension)	Omit dose until recovery to asymptomatic bradycardia or to a heart rate ≥60 bpm If the concomitant medication can be adjusted or discontinued, resume 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

[redacted]

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

* Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. All dose modifications should be based on the worst preceding toxicity.
** If Grade 3 or 4 hyperbilirubinemia is due to the indirect (non-conjugated) component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then ↓ 1 dose level and continue treatment at the discretion of the investigator.
***LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin > 2.0 x ULN), alkaline phosphatase 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 6.2.4.4)
***** 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 6.2.4.5)

[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.

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)	ALT/AST/total bilirubin 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) ALT/AST/total bilirubin ≥ 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 Patients with liver metastasis and grade 2 AST/ALT at baseline, increased monitoring is required; for grade 3 or 4 AST/ALT follow guidelines for grade 3 or 4 AST/ALT
Investigations (renal)	Serum creatinine Grade 2: Test weekly (or more frequent) until Grade 1 Thereafter, test every cycle (4 weeks) Serum creatinine ≥ Grade 3: Test twice weekly (or more frequent) until ≤ Grade 1 Thereafter, test every cycle (4 weeks)
Investigations (pancreatic)	Amylase/lipase ≥ Grade 3: Test weekly (or more frequently) until ≤ Grade 1. After resumption of dosing, continue to test weekly for one additional cycle (4 weeks). If no reoccurrence of ≥ Grade 2 event, continue monitoring every cycle (4 weeks)
*Note: this table refers only to the evaluation schedule to monitor selected toxicities. Refer to Table 6-3 for dose modifications required for applicable toxicities	

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 liver 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 ≤

[redacted]

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. For patients with liver metastasis and grade 2 AST/ALT at baseline, increased monitoring is required; for grade 3 and 4 AST/ALT; follow guidelines for grade 3 or 4 AST/ALT.

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

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

Refer to Table 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
- 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.

[redacted]

- 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.
- [redacted]
- 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 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 descried in Table 6-3.

6.2.4.4 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]

6.2.4.5 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.
- 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 sub-cutaneous 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.

6.2.4.6 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.

[redacted]

6.2.4.7 Guidelines for the treatment of hypophosphatemia

In the phase I study [CLDK378X2101], as of [redacted] there were 9 cases of grade 3 hypophosphatemia in all dose groups, one of which was a DLT that contributed to the MTD determination – this patient was able to continue LDK378 at the same dose. One patient in the 750 mg group had grade 3 hypophosphatemia that resolved after dose adjustment or interruption; in the remaining 8 cases, patients were able to continue therapy without dose modification. Hypophosphatemia was a commonly reported AE (6.3%), regardless of relationship to LDK378 treatment.

Therefore, phosphate levels will be checked at baseline and during treatment. In cases of hypophosphatemia at baseline, phosphate supplements should be started before treatment with LDK378. For any grade of hypophosphatemia during the study, treatment with phosphate supplements should be given as clinically indicated, and the LDK378 dose can be maintained.

6.2.4.8 Recommendations for the monitoring of cases of interstitial lung disease (ILD)/pneumonitis toxicity

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

Exclude other cases of pneumonitis, and follow dose modification guidelines as described in Table 6-3.

6.2.4.9 Anticipated risks and safety concerns of the study treatment

Appropriate eligibility criteria, 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 IB.

6.3 Concomitant medications

In general, the use of any concomitant medication/therapy deemed necessary for the care of the patient (e.g. anti-emetics, anti-diarrheal) 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 over-the counter medications, herbal medications (prohibited, see Section 6.3.2.7), food or vitamin supplements.

[redacted]

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. If possible, systemic corticosteroid treatment should not be given during the study, except for:

- Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular);
- Stable doses of corticosteroid therapy such as dexamethasone and prednisone (e.g. for tumor associated symptoms) are permitted during the course of the study.

6.3.1.2 Drugs that are metabolized by CYP450 enzymes

[redacted]

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 I). Duration of concomitant treatment should be kept as short as possible (e.g. less than 1 week), or completely avoided whenever possible. Patients receiving such medications must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require 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 I), except for drugs which have narrow therapeutic index/sensitive substrates for these CYP isoforms (refer to Section 6.3.2.6 and Table 14-1 of Appendix I).

6.3.1.3 Non-enzyme inducing anti-epileptic drugs

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

6.3.1.4 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 LDK378 therapy, as determined by the Investigator may undergo

[redacted]

radiotherapy and/or surgical resection as palliative localized therapy to treat metastatic lesions. LDK378 should be held for at least 4 days prior to radiotherapy and at least 1 day prior to any surgery. LDK378 may be resumed ≥3 days after completing radiotherapy or minor surgery, and ≥2 weeks after major surgery.

6.3.1.5 Gastric protection agents

The use of gastric protection agents including antacids, H2-antagonists, and proton pump inhibitors (PPIs; Table 14-2 of Appendix I) 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).

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 and palliative surgery as described in Section 6.3.1.4], and anti-cancer surgery) other than the study treatment must not be given to patients while they are enrolled in the treatment portion of the trial. If such agents are required then the patient must be permanently discontinued from the treatment portion of the study.

6.3.2.2 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

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

6.3.2.4 Enzyme inducing anti-epileptic drug (EIAED)

Use of EIAEDs is not permitted. Refer to Table 14-3 of Appendix I 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.

[redacted]

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 14-3 of Appendix I 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 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 14-3 of Appendix I for a list of these medications. Please note that this list may not be comprehensive.

6.3.2.7 Herbal medications

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

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

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

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

Concomitant use of LDK378 and any medication included in Appendix 1, Table 14-4 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.

[redacted]

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 identified for pre-screening and is retained as the primary identifier for the patient throughout the entire participation in the trial. The Subject No. consists of the center number (Center No.) as assigned by Novartis to the investigative site with a sequential patient number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the Informed Consent Form (ICF), the patient is assigned to the next sequential Subject No. available to the investigator through the Oracle Clinical RDC interface. Once assigned, the Subject No. must not be reused for any other subject.

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

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. At the C1D1 visit, before the patient receives the first dose, the IRT system must again be contacted to enroll the patient in the study. 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

[redacted]

6.5.1 Study drug packaging and labeling

[redacted]

6.5.2 Drug supply and storage

[redacted]

6.5.3 Study drug compliance and accountability

6.5.3.1 Study drug compliance

[redacted]

6.5.3.2 Study drug accountability

[redacted]

6.5.3.3 Handling of other study treatment

Not applicable.

[redacted]

6.5.4 Disposal and destruction

[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 patient's source documentation. eCRF will not 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	Screening Phase		Treatment Phase				Post treatment efficacy/ follow up phase		Survival follow-up phase
					Cycle 1 (28 d)		Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Molecular pre-screen**	**Screening Visit (Day -28 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**Study phase completion**	**Survival follow-up**
Obtain pre-screening informed consent	D		X								
Obtain Main Informed Consent	D	11.3.		X							
[redacted]											
Confirmation of ALK status by central laboratory	D	7.1.1.	New biopsy preferred and/or archival tissue & pathology report								
End of Phase Disposition Page	D	7.1.		X				X		X	
Patient history											
Demography	D	7.1.2.3.		X							
Inclusion/ exclusion criteria	D	5.2. 5.3.		X							
Eligibility check	S	7.1.2.1.		X							
Relevant medical history/ current medical conditions	D	7.1.2.3.		X							

[redacted]

	Category	Protocol section	Screening Phase		Treatment Phase				Post treatment efficacy/ follow up phase		Survival follow-up phase
					Cycle 1 (28 d)		Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Molecular pre-screen**	**Screening Visit (Day -28 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**Study phase completion**	**Survival follow-up**
Diagnosis and extent of cancer	D	7.1.2.3.		X							
Prior antineoplastic therapies (meds, surgery, radiation)	D	7.1.2.3.		X							
Prior and concomitant medications	D	6.3.		Continuous							
Physical examination	S	7.2.2.1.		X	X	X	X	X			
Performance status (WHO)	D	7.2.2.4.		X	X		X	X			
Height	D	7.2.2.3.		X							
Weight	D	7.2.2.3.		X	X		X	X			
Vital signs	D	7.2.2.2.		X	X	X	X	X			
Laboratory assessments											
Hematology	D	7.2.2.5.1.		X	X	X	X	X			
Blood chemistry	D	7.2.2.5.2.		X	X	X	X	X			
Urinalysis (dipstick) with micro-analysis	D	7.2.2.5.3.		X							
Pregnancy test	D	7.2.2.5.4.		X	X		X	X			
Testosterone, LH, FSH, sex hormone binding globulin (SHBG) (males only)	D	7.2.2.5.5.		X	X	X					
Coagulation	D	7.2.2.5.6.		X							

[redacted]

	Category	Protocol section	Screening Phase		Treatment Phase				Post treatment efficacy/ follow up phase		Survival follow-up phase
					Cycle 1 (28 d)		Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Molecular pre-screen**	**Screening Visit (Day -28 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**Study phase completion**	**Survival follow-up**
Imaging											
CT scan or MRI of chest and abdomen	D	7.2.1.		X			Cycle 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							
CT scan or MRI of brain	D	7.2.1.		X			Cycle 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)		

[redacted]

	Category	Protocol section	Screening Phase		Treatment Phase				Post treatment efficacy/ follow up phase		Survival follow-up phase
					Cycle 1 (28 d)		Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Molecular pre-screen**	**Screening Visit (Day -28 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**Study phase completion**	**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)			Cycle 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)		
Study drug administration											
LDK378 dosing	D	6.1.			Continuous						
Safety											
Adverse events	D	8.1.		Continuous							
ECG	D	7.2.2.6.1.		X	X	X	X	X			
[redacted]											

[redacted]

	Category	Protocol section	Screening Phase		Treatment Phase				Post treatment efficacy/ follow up phase		Survival follow-up phase
					Cycle 1 (28 d)		Subsequent cycles (28 d)	End of study treatment (EOT)			
Visit name			**Molecular pre-screen**	**Screening Visit (Day -28 to Day -1)**	**Cycle 1 Day 1**	**Cycle 1 Day 15**	**Cycle 2 Day 1; Cycle 3 Day 1; etc.**	**End of treatment visit**	**Tumor follow-up**	**Study phase completion**	**Survival follow-up**
Biomarker studies											
[redacted]											
Survival follow-up											
Antineoplastic therapies since discontinuation of study treatment	D	7.1.4.1.							X		X
Survival assessment		7.1.4.1.									X

[redacted]

7.1.1 Pre-screening

Prescreening will involve all activities until the determination of ALK status by the central laboratory.

Patients will be consented for a pre-screening visit. If a patient is being treated with chemotherapy for their NSCLC, pre-screening may be performed during the chemotherapy treatment. However, if a patient is determined to be ALK positive, the patient must only be screened when progression of disease on chemotherapy treatment (if such treatment is being used) is confirmed.

Preferably, a newly obtained tumor biopsy should be submitted for all patients to determine ALK status and trial entry eligibility. If the new biopsy cannot be obtained, a formalin-fixed paraffin-embedded (FFPE) tumor sample(s) from archival material obtained at the time of diagnosis of NSCLC or any time since must be submitted for central analysis. Analysis material must be sent immediately upon the patient entering molecular pre-screening. If unstained slides cannot be prepared, paraffin blocks can be submitted. Sections will be cut from paraffin block and the remaining material will be returned to the site upon request. The translocation analysis to confirm ALK rearrangement will be the FDA-approved FISH test (Abbott Molecular Inc) using Vysis break-apart probes.

ALK status must be determined centrally prior to screening assessments being performed. Instructions for tumor sampling, preparation and packing are described in a separate laboratory manual. Molecular pre-screening samples must consist of tumor tissue (which may include fine-needle aspirates) but cannot consist of a cytology sample obtained from fluid collections (e.g. pleural, pericardial or ascitic effusions), as the FDA-approved FISH test is not validated on such samples.

Results of the assay will be sent to the site. If delays are experienced in processing the sample, the pre-screening site will be informed. Results of the ALK rearrangement status must be received before the patient is permitted to attend the screening visit.

7.1.2 Screening

Screening assessments to confirm eligibility should be performed as per the schedule of assessments. Written informed consent must be obtained before any study specific procedure is performed.

Re-screening of patients will not be allowed, but laboratory parameters which do not meet the inclusion criteria may be re-tested within the 28 day screening window.

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
- NSCLC diagnosis and extent of disease, including:
  - Date of diagnosis and stage of NSCLC
  - ALK status documentation using the FDA-approved Vysis ALK break-apart FISH assay. ALK status must be confirmed using the FDA-approved Vysis ALK break-apart FISH test via a central laboratory using the new biopsy obtained prior to study entry (if biopsy was taken) or, if a new biopsy is not available, using the required archival tumor tissue.
  - Site of active disease
  - Characteristics of disease
- Prior antineoplastic therapies (medications, radiation, surgeries)
- 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 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 as assessed by the investigator), LDK378 administration may be stopped, or may be continued if the patient is continuing to derive clinical benefit in the opinion of the investigator (see Section 6.1.3).

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

[redacted]

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 timepoints.

7.1.4 Discontinuation of study treatment

7.1.4.1 Patients discontinuing LDK378

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

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

Study treatment must be discontinued under the following circumstances:

- Emergence of adverse events, as described in Section 6.3
- Laboratory abnormalities, as described in Section 6.3
- Pregnancy
- Deviations from the prescribed dose regimen, as described in Section 6.2.3
- Use of prohibited treatment, as described in Appendix 1 for LDK378
- Any other protocol deviation that results in a significant risk to the patient's safety
- Study Terminated by Sponsor
- Patient/guardian decision
- Physician decision
- Lost to follow-up
- Death

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Section 7.2.1 and enter the survival follow-up period or continue tumor assessments as appropriate. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them as specified in Section 7.1.6.

End of treatment visit

Patients who discontinue LDK378 should be scheduled for a visit as soon as possible and within 7 days of the last dose of LDK378, 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. As a minimum, all patients who discontinue LDK378, including those who refuse to return for a final visit, will be contacted for safety evaluations at least 30 days after the last dose of LDK378. The investigator should inquire about any AE observed/concomitant medication taken during this 30-day period. This 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 LDK378.

7.1.4.2 Withdrawal of consent

[redacted]

7.1.5 Follow-up period

7.1.5.1 Post-treatment efficacy follow-up

If a patient discontinues study treatment in the absence of confirmed PD, tumor assessments every 8 weeks should continue to be performed from the EOT visit until PD is assessed by the investigator (see Section 7.2.1.2); however, safety assessments do not need to continue to be performed. -Antineoplastic therapies since discontinuation of study treatment will continue to be collected.

Once the patient ceases tumor follow-up, the reason for completion should be recorded on the Study Phase Completion Disposition eCRF page.

7.1.5.2 Survival follow-up

Following the end of tumor follow-up for efficacy (i.e. after the time of confirmed PD), the patient will be contacted every 3 months to determine survival status and antineoplastic therapies since discontinuation of study treatment.

7.1.6 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

[redacted]

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.

7.2 Assessment types

7.2.1 Efficacy assessments

Tumor evaluation will be determined locally according to the Novartis guideline (Appendix II) on the Response Evaluation Criteria in Solid Tumors (RECIST), based on RECIST Version 1.1 (Eisenhauer et al 2009). The investigator's assessment will be used for the primary endpoint analysis and for patient's treatment decision making.

Imaging data will be centrally collected and checked for quality by an imaging Clinical Research Organization (CRO) designated by Novartis. It will undergo review by a blinded independent review committee (BIRC) according to the Novartis guideline (Appendix II) on the Response Evaluation Criteria in Solid Tumors (RECIST), based on RECIST Version 1.1.

Full details of the central reading process are included in the BIRC Charter.

7.2.1.1 Baseline assessments

Details of imaging requirements and logistics can be found in the separate Imaging Manual.

Tumor evaluation will be performed at baseline within 28 days of, and prior to, enrollment. 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 1.1 (Appendix II). Measurable lesions include lytic or mixed (lytic + blastic) bone lesions with an identifiable soft tissue component that meets the measurability criteria per RECIST 1.1 (Appendix II).
- 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) with IV contrast or Magnetic Resonance Imaging (MRI) of chest and upper abdomen.
  - The preferred radiologic technique is CT with intravenous (IV) 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 upper abdomen should be performed.
- 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)).
  - After screening, scans need not be repeated, unless clinically indicated. If indicated, the same methodology as at screening should be used.
- 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).
  - After screening, scans need not be repeated, unless clinically indicated. If indicated, the same methodology as at screening should be used.
- Brain CT with IV contrast or MRI scan.
  - After screening, scans need not be repeated, unless clinically indicated. If indicated, the same methodology as at screening should be used.
- Color photographs (with a metric ruler) if skin lesions are present.
  - After screening, scans need not be repeated, unless clinically indicated. If indicated, the same methodology as at screening should be used.
- CT or MRI of any other site of disease not captured by any of the above listed images (e.g., pelvis, neck).
  - After screening, scans need not be repeated, unless clinically indicated. If indicated, the same methodology as at screening should be used.

Any imaging assessments already completed during the regular work-up of the patient within 6 weeks prior to start of treatment, including before signing the main study ICF, can be considered as the baseline images for this study.

Chest x-ray or ultrasound must 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.**

[redacted]

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 upper 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 upper abdomen CT/MRI (and pelvis CT/MRI if applicable). Whole body bone scans need not be repeated after baseline unless clinically indicated.
- Brain CT with IV contrast 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 and the BIRC review promptly after acquisition. The activities of the imaging CRO and the BIRC will be described in the Imaging Charter.

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 II).

Imaging evaluations will 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.

Imaging assessment by the BIRC

All radiological assessments will be read locally and should be submitted promptly after acquisition to the imaging CRO designated by Novartis. The process at the imaging CRO will ensure that the BIRC remains blinded to the results of the local assessment (and other unblinding information). The decision regarding patient management will remain with the local investigator.

[redacted]

Rapid image transmission to the BIRC may be accomplished by uploading all digital images acquired by the investigator in a secured website.

The results of the BIRC assessment will not be communicated to sites.

All timepoints will be read on an ongoing basis (rolling reads) as detailed in the imaging charter to be provided by the designated imaging CRO.

Duration of post-baseline tumor assessments

Tumor assessments will continue until one of the following events:

- The patient experiences RECIST-defined PD as determined by the investigator AND treatment with LDK378 ceases. If treatment with LDK378 continues beyond RECIST-defined PD, imaging assessments must continue every 8 weeks until LDK378 treatment ceases
- If a patient discontinues study treatment in the absence of PD, tumor assessments will continue to be performed every 8 weeks until the patient experiences a RECIST-defined PD as determined by the investigator
- Death
- Lost to follow-up, or
- Patient decision involving withdrawal of consent (see Section 7.1.4.1).

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.

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 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 medication 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 as safety monitoring. All unscheduled blood testing will be performed locally. Dipstick urinalysis will be performed locally, except in the case of any out of range parameter on scheduled local urine analysis, when a urine sample will be sent to central laboratory for further analysis. Details on the collection, shipment of blood, urine and tumor samples and reporting of results by the central laboratory are provided to investigators in a separate [Laboratory Manual]. The time windows granted for laboratory evaluations are identical to the corresponding visit time windows for each visit (refer to Section 7.1).

Laboratory values obtained at the screening visit will be used to assess eligibility to meet inclusion criteria 7. In addition, eligible patients must have baseline laboratory assessments performed on Cycle 1 Day 1 / Run-in Day 1 or within 24 hours prior to dosing. The results of centrally-analyzed laboratory assessments performed at Cycle 1 Day 1 do not need to be received by the site prior to initiation of dosing.

[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), 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, GGT, lipase
Urinalysis	Macroscopic panel (dipstick) (bilirubin, blood, glucose, ketones, WBC, pH, protein, specific gravity) Microscopic panel (RBC, WBC, casts)
Hormones (males only)	Testosterone, LH, FSH, sex hormone binding globulin (SHBG)
Coagulation	INR and pro-thrombin time (PT) or Quick Test

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

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 Blood 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

All women of childbearing potential must complete a serum pregnancy test at the screening visit, at Cycle 1 Day 1, at every cycle throughout the study and at End of Treatment. Central laboratories will be used for the analysis of serum pregnancy tests.

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 bilateral 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 as part of the study assessments).

[redacted]

The time windows granted for pregnancy testing are identical to the corresponding visit time windows for each visit. Refer to Table 7-1.

7.2.2.5.5 Hormones

Testosterone, LH, FSH and sex 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

INR and pro-thrombin time (PT) or Quick Test will be measured at screening only.

7.2.2.6 Cardiac assessments

7.2.2.6.1 Electrocardiogram (ECG)

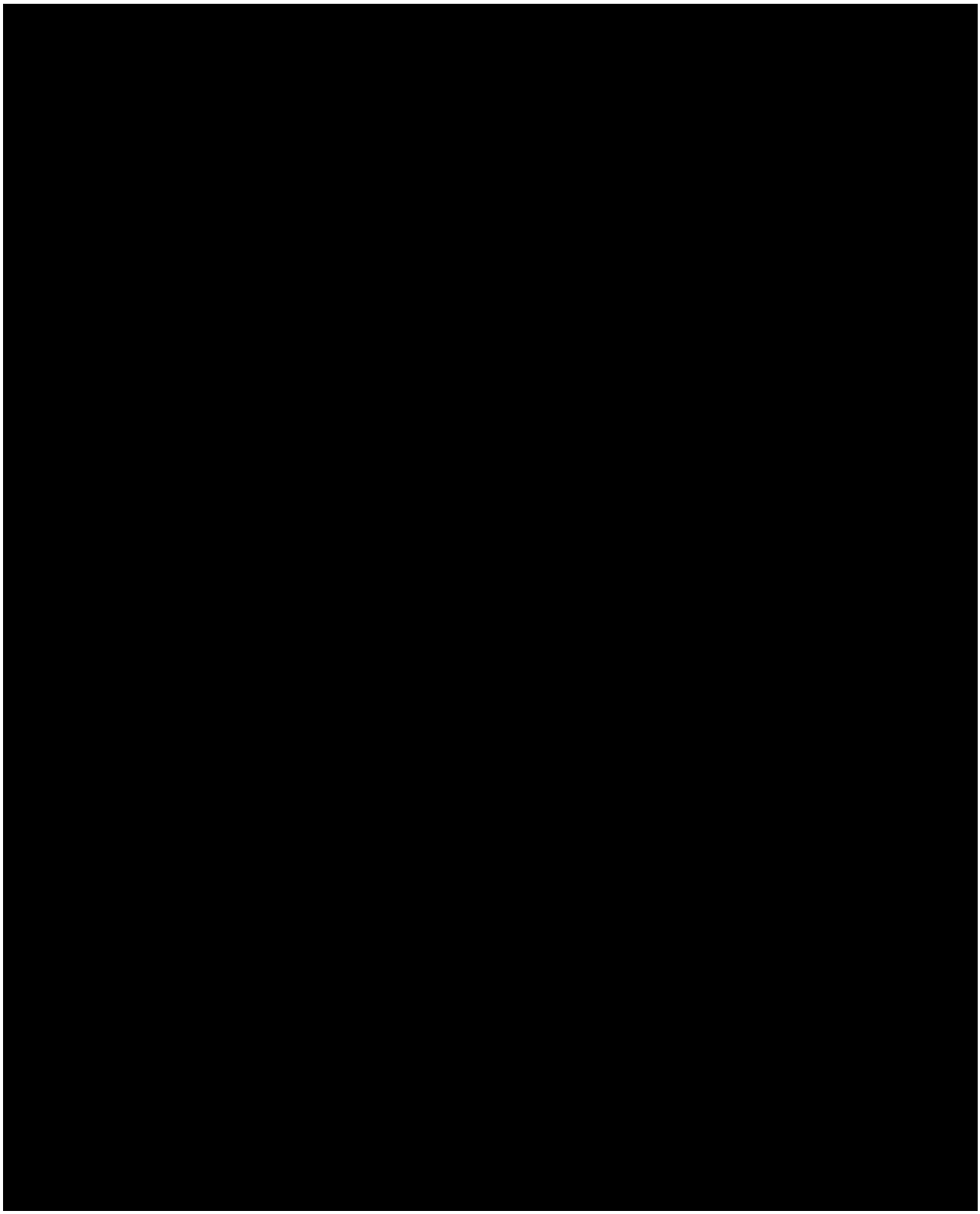
A standard 12 lead ECG will be performed

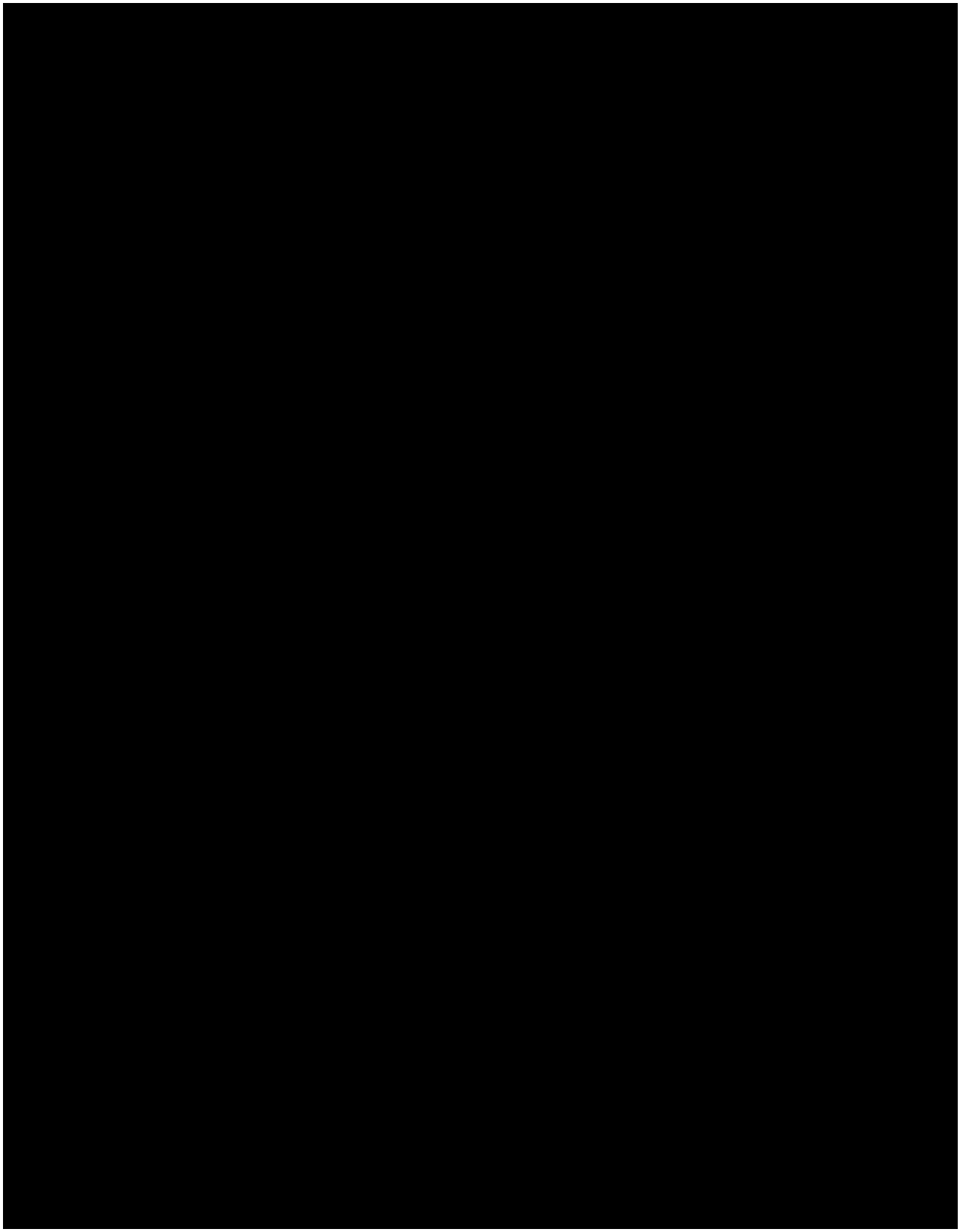
- At the screening visit, in triplicate.
- At Cycle 1 Day 1, in triplicate, pre-dose, and in triplicate 6 hours (+/- 30 minutes) after dosing.
- At Cycle 1 Day 15 and at Cycle 2 Day 1 in triplicate, pre-dose.
- [redacted]
- At other defined timepoints (Day 1 of subsequent cycles) (see Table 7-1) as single ECGs, pre-dose.

ECGs will be performed in supine position. All ECGs recorded for each time point 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.

Interpretation of the tracing must be made by a qualified physician. 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. 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 significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page. When triplicate ECGs are taken, for the purposes of inclusion criteria and dose level management, mean parameter values should be used.

[redacted]





[redacted]

[redacted]

7.2.5 Resource utilization

Not applicable.

[redacted]

[redacted]

[redacted]

8 Safety monitoring and reporting

8.1 Adverse events (AEs)

8.1.1 Definitions and reporting

An AE 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 AEs 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).

AEs that begin or worsen after informed consent has been obtained should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's eCRF. AE monitoring should be continued for at least 30 days following the last dose of study treatment. AEs (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 AE.

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

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)

[redacted]

3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)
7. Whether it is serious, where a serious AE (SAE) is defined as in Section 8.2.1.

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

Once an AE 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), should not be reported as a SAE.

AEs 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 AE 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 eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs 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 AE should not be reported as AEs. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate an SAE unless it meets the definition of seriousness below and/or at the investigator's discretion. A dose hold or medication for the laboratory abnormality may be required by the protocol in which case the laboratory abnormality would, by definition, be an AE and must be reported as such (see Section 6.2).

[redacted]

8.1.3 Adverse events of special interest

Adverse events of special interest to be monitored for LDK378 have also been identified and include: hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, bradycardia, hyperglycemia gastrointestinal toxicity (nausea, vomiting and diarrhea) and pancreatitis (including lipase and amylase elevations).

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

8.2 Serious adverse events

8.2.1 Definitions

An SAE is defined an AE characterized by 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
- Protocol exempt SAEs: Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (RECIST criteria), should not be reported as 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 SAE experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE

occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the SAE submission process and requirements for signatures are to be found in the investigator folder provided to each siteFollow-up information is submitted in the same way as the original SAE Report Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study treatment, an oncology Novartis 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 (EC) 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

Patients who become pregnant during the trial will be withdrawn from the study.

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed until 3 months following delivery 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.

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

[redacted]

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 (DMC)

An independent Data Monitoring Committee (DMC) will be constituted and will be responsible for monitoring and reviewing the clinical study data for efficacy and safety during the study prior to the final data analysis. Efficacy data will be reviewed periodically during Stage 1 to advise on whether the trial should proceed to Stage 2 and full enrolment. DMC review for the purpose of advising on the transition of the trial from Stage 1 to Stage 2 will be based primarily on local investigator assessment of response. However, the DMC may request data on assessment of response by the BIRC if deemed necessary. Responsibilities of the DMC, communication flow between DMC, Steering Committee and Novartis, and timing of data safety and efficacy reviews, will be included in the DMC charter document.

It is envisioned that the DMC may make four types of recommendations, namely:

1. Transition into Stage 2 of the trial or stopping enrollment after stage 1 for futility
2. No safety or ethical issues, ethical to continue the trial as planned
3. Serious safety concerns precluding further study treatment, regardless of efficacy
4. Ethical to continue the study but recommend an amendment to the protocol (e.g. incorporate a safety analysis).

8.7 Steering Committee (SC)

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 DMC, SC and Novartis will be included in the SC charter document.

9 Data collection and management

[redacted]

9.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, Novartis personnel (or designated CRO) will review the protocol and eCRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, adherence to the protocol and 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 eCRFs 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 eCRF 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 eCRFs are performed according to the study-specific monitoring plan.

[redacted]

10 Statistical methods and data analysis

The data from all participating centers in this protocol will be combined. The primary analysis of study data will be conducted at the time when all patients have either completed at least six cycles of treatment or discontinued treatment. These data will be summarized in the primary Clinical Study Report (CSR). The final analysis of study data will be conducted at the end of the study (see Section 4.3). All available data from all patients up to this cutoff date will be analyzed. Additional data from patients continuing to receive study treatment after this time will be captured by a separate protocol. Efficacy and safety reports will be reviewed by a DMC regularly during the conduct of the study (see Section 8.6 for details).

10.1 Analysis sets

10.1.1 Full Analysis Set

The Full Analysis Set (FAS) will include all patients who receive at least one dose of LDK378. Patients who are screened but never started treatment will be listed.

The FAS will be used for all listings of raw data. Unless otherwise specified the FAS will be the default analysis set used for all analyses, including the primary analysis.

10.1.2 Safety Set

The Safety Set will include 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 will include 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).

[redacted]

[redacted]

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, 25th and 75th percentiles, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

The actual dose and duration in days of 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 intensity), will be listed and summarized for all patients.

Dose reductions and dose interruptions (including the reasons for these) will be listed and summarized.

The safety set will be used.

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

10.4 Primary objective

The primary objective is to evaluate the anti-tumor activity of LDK378.

10.4.1 Variable

The variable used to evaluate the anti-tumor activity of LDK378 is the overall response rate (ORR), 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 (Appendix II).

10.4.2 Statistical hypothesis, model, and method of analysis

The primary analysis will be performed on the FAS.

The study targets an ORR of 50%. A response rate of 35% or less is considered as insufficient level of activity for the proposed patient population. Therefore, a null hypothesis of ORR $\leq$ 35% vs. an alternative hypothesis of ORR>35% will be tested using a one-sided test with alpha of 0.05 based on a Simon's optimal two-stage design (Simon 1989). If 45 or more responses are seen in 105 total patients (estimated ORR of 42.9%), then the null hypothesis will be rejected and the trial declared positive.

Stage 1 will enroll 43 patients. If the study is terminated early at the end of Stage 1 (16 or fewer responses among 43 patients enrolled to Stage 1), then the study will be considered to have failed to reject the null hypothesis. See Section 10.7 for further details of the stopping

[redacted]

criteria for futility. Stage 2 will include an additional 62 patients. The primary analysis will occur when all 105 patients have completed 6 cycles of treatment or discontinued treatment earlier.

The ORR will be estimated and the 90% exact confidence interval (CI) will be provided. The uniformly minimum variance unbiased estimator (UMVUE) and the 90% two-stage CI (Atkinson and Brown 1985) will also be presented.

10.4.3 Handling of missing values/censoring/discontinuations

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.

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.

10.4.4 Supportive analyses

The primary analysis on the FAS will be repeated on the PPS.

ORR, per RECIST 1.1, as assessed by the BIRC, will also be estimated and CIs will be provided based on the FAS as described in Section 10.4.2.

10.5 Secondary objectives

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

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

No adjustment for multiple testing will be made.

10.5.1 Key secondary objective(s)

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 may be described using Kaplan-Meier curves and relevant statistics if appropriate. Censoring rules for DOR are described in the Appendix II.

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. TTR will be described using Kaplan-Meier methods and appropriate summary statistics. The TTR analysis will be conducted with censoring rules as described in the Appendix II.

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 90% CI provided. DCR will be estimated.

10.5.2 Other secondary efficacy objectives

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 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 and the BIRC 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 and by BIRC.

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. All listings and tables will be presented for all patients.

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

[redacted]

1. Pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
2. On-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
3. Post-treatment period: starting at day 31 after last dose of study medication.

10.5.3.2 Adverse events (AEs)

Summary tables for AEs will include only AEs that started or worsened 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 post-treatment period will be flagged.

The incidence of AEs will be summarized by system organ class and/or preferred term, maximum severity (based on Common Terminology Criteria for Adverse Events [CTCAE] grades version 4.03), and relation to study drug.

Clinically notable adverse events (CNAEs) 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 CNAE, number and percentage of patients with at least one event in each CNAE category will be reported.

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.

A listing of laboratory values will be provided by laboratory test, patient, and study day. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory abnormalities).

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.

[redacted]

Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges will be generated.

[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 for baseline to worst on-treatment result based on notable parameter categories
- 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.

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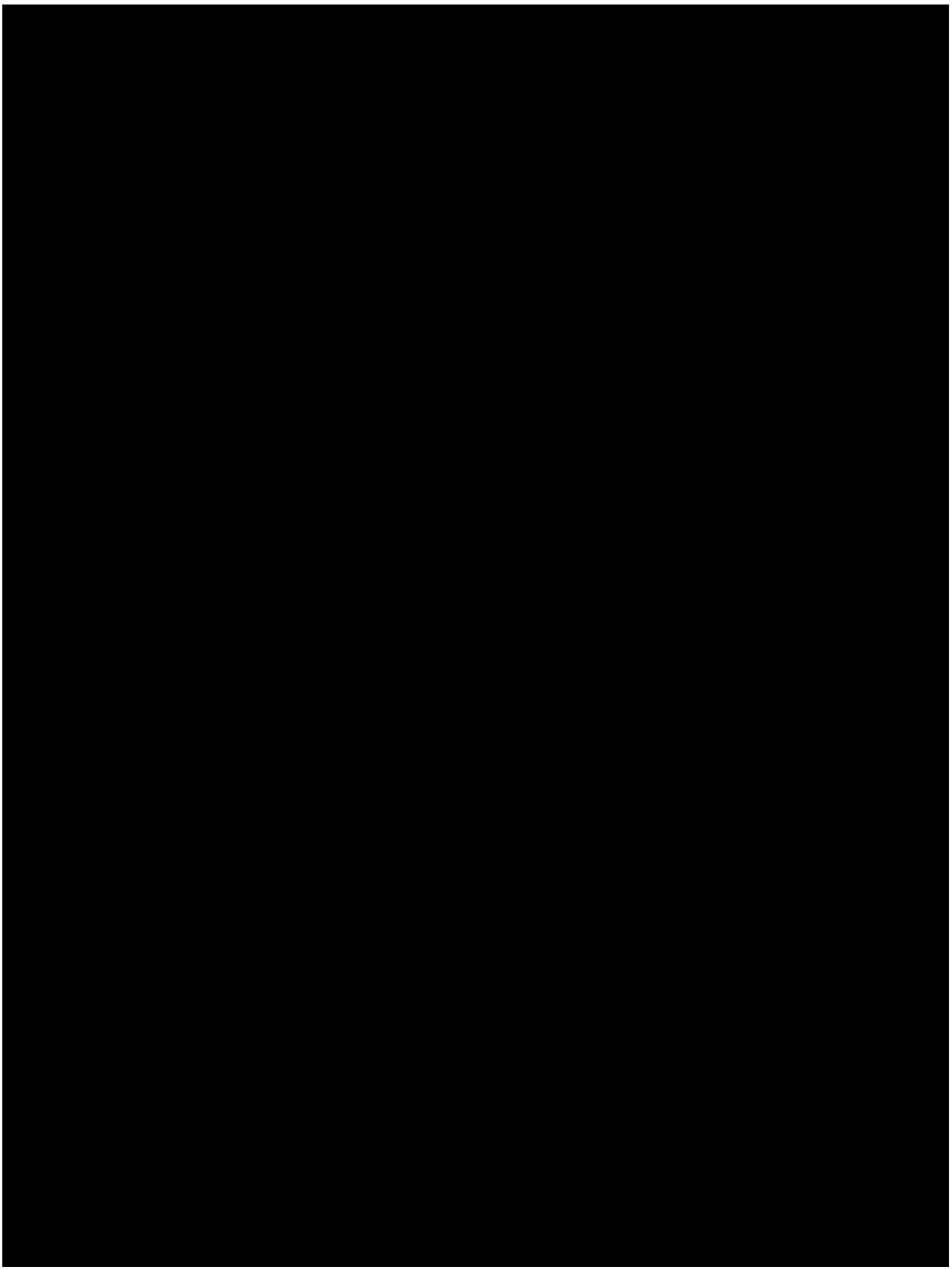
[redacted]



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10.7 Interim analysis

In order to inform the recommendation to proceed to Stage 2 of the study, the DMC will periodically review response data during Stage 1, based on local investigator assessment, as defined in the DMC charter (see Section 8.6). The DMC may request data of assessment of response by the BIRC if deemed necessary to provide its recommendation. As per Simon's optimal two-stage design, the trial will be stopped at Stage 1 for futility if 16 or fewer responses are observed in the 43 patients enrolled to Stage 1. According to this rule, the DMC will make the recommendation to transition into the Stage 2 of the study. If at the time that the last patient is enrolled to Stage 1 a minimum of 17 responses have not yet been observed, accrual may be temporarily suspended until either the minimum number of 17 responses are observed or all 43 patients have been followed for at least 6 cycles of LDK378 or discontinued treatment.

[redacted]

Safety will be reviewed by a DMC regularly during the conduct of the study, as outlined in the DMC charter document (see Section 8.6).

10.8 Sample size calculation

Based on Simon's (1989) optimal two-stage design, if the true ORR is 50% (under the alternative hypothesis), approximately 105 total patients are required to reject the null hypothesis of ORR $\leq$ 35% with a one-sided alpha of 0.05 and 90% power. If at least 17 confirmed responses are observed among 43 patients enrolled into Stage 1, an additional 62 patients will be enrolled into Stage 2. If 45 or more confirmed responses are observed among 105 total patients, the trial will be declared positive.

The operating characteristics of the design are described in Table 10-1.

Table 10-1 Operating characteristics of Simon's optimal two-stage design

	True ORR			
	35% (null hypothesis)	**40%**	**45%**	**50% (alternative hypothesis)**
Probability stop for futility at Stage 1 (16 or fewer responses out of 43 patients enrolled at Stage 1)	0.683	0.418	0.192	0.063
Probability trial is success (45 or more responses out of 105 total patients)	0.049	0.268	0.642	0.900

10.9 Power for analysis of key secondary variables

Not applicable.

11 Ethical considerations and administrative procedures

11.1 Regulatory and ethical compliance

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

11.2 Responsibilities of the investigator and IRB/IEC/REB

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

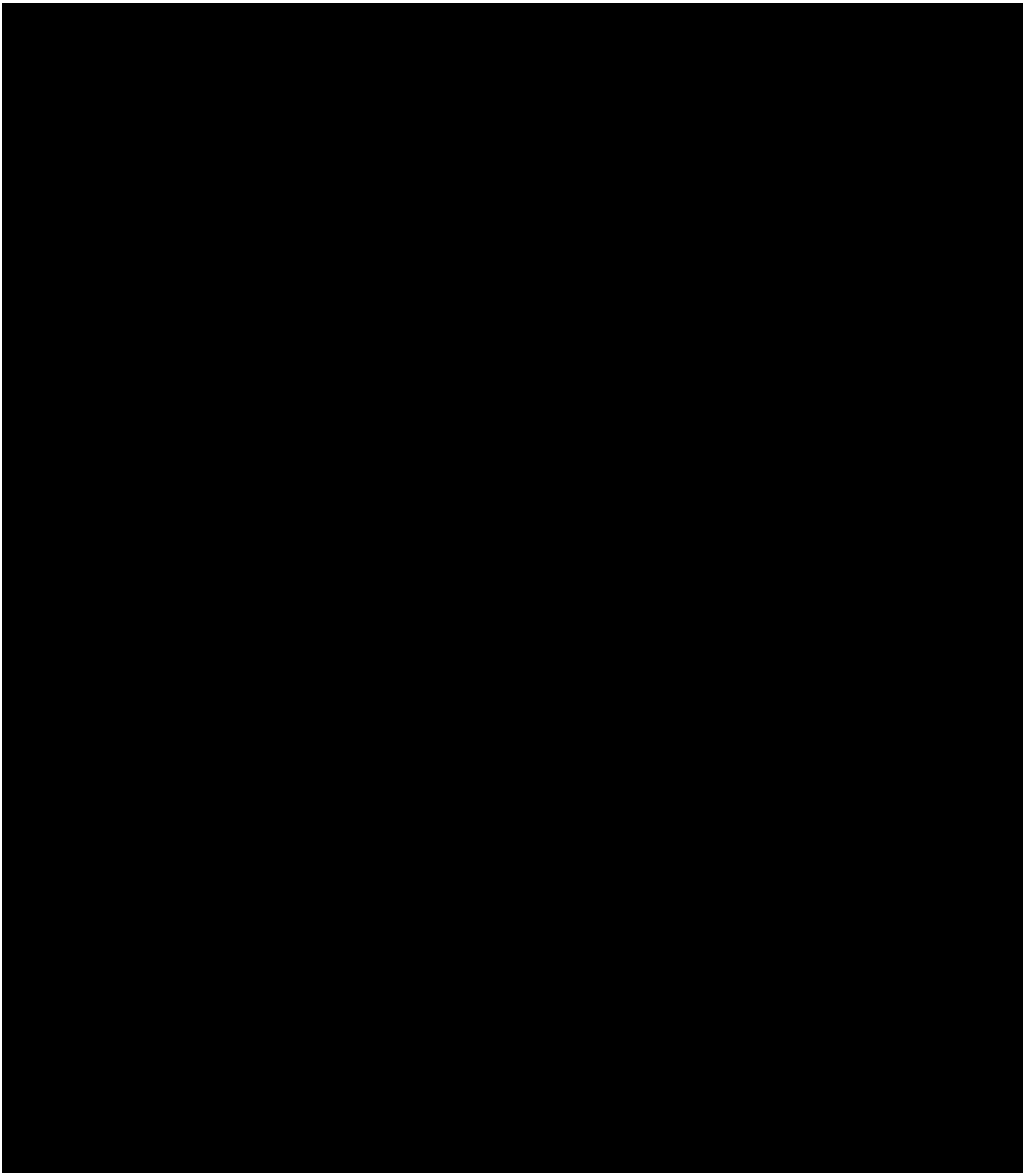
[redacted]

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 4.2.

11.5 Publication of study protocol and results

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



11.8 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.

13 References (available upon request)

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14 Appendices

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

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

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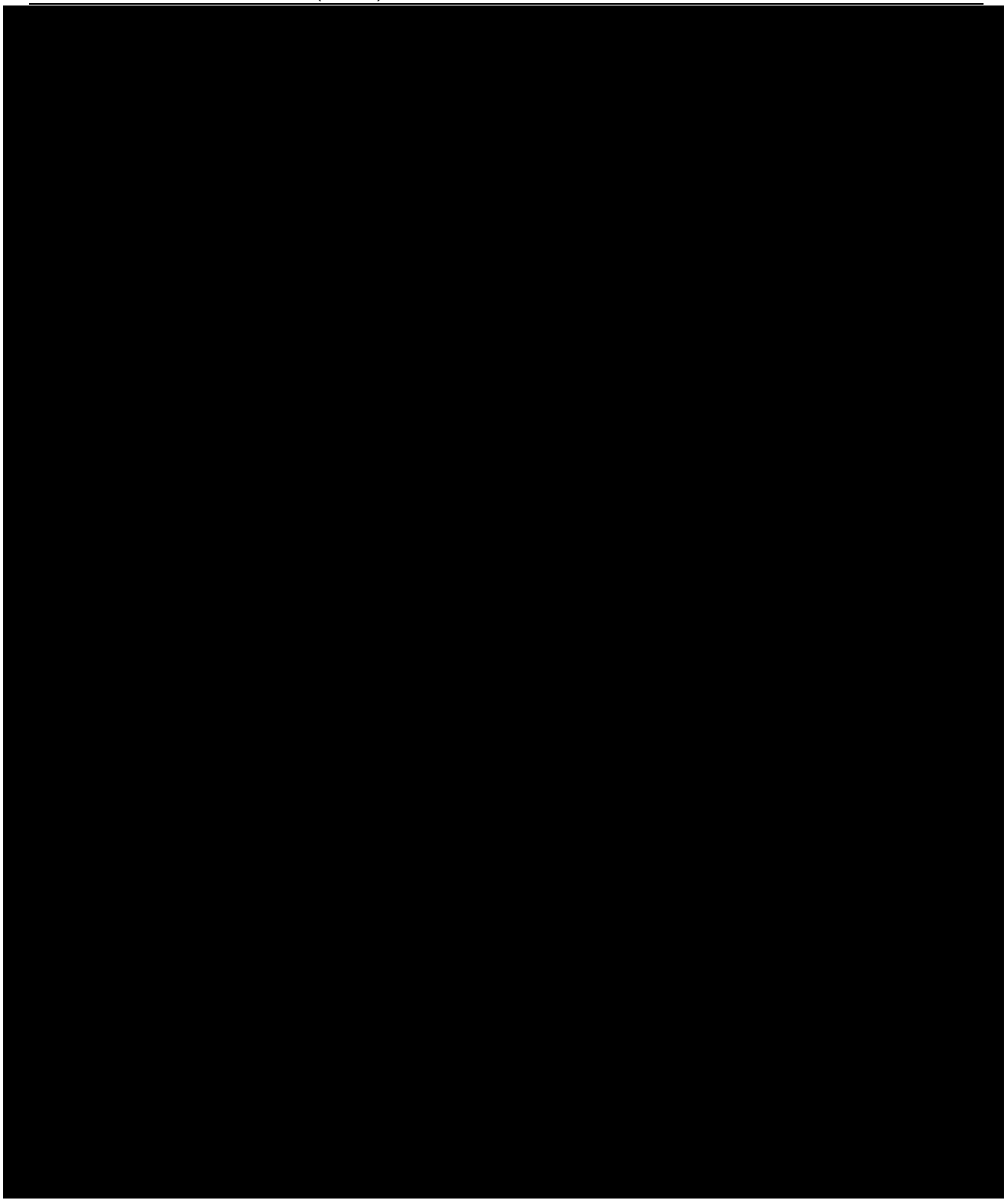

Glossary

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

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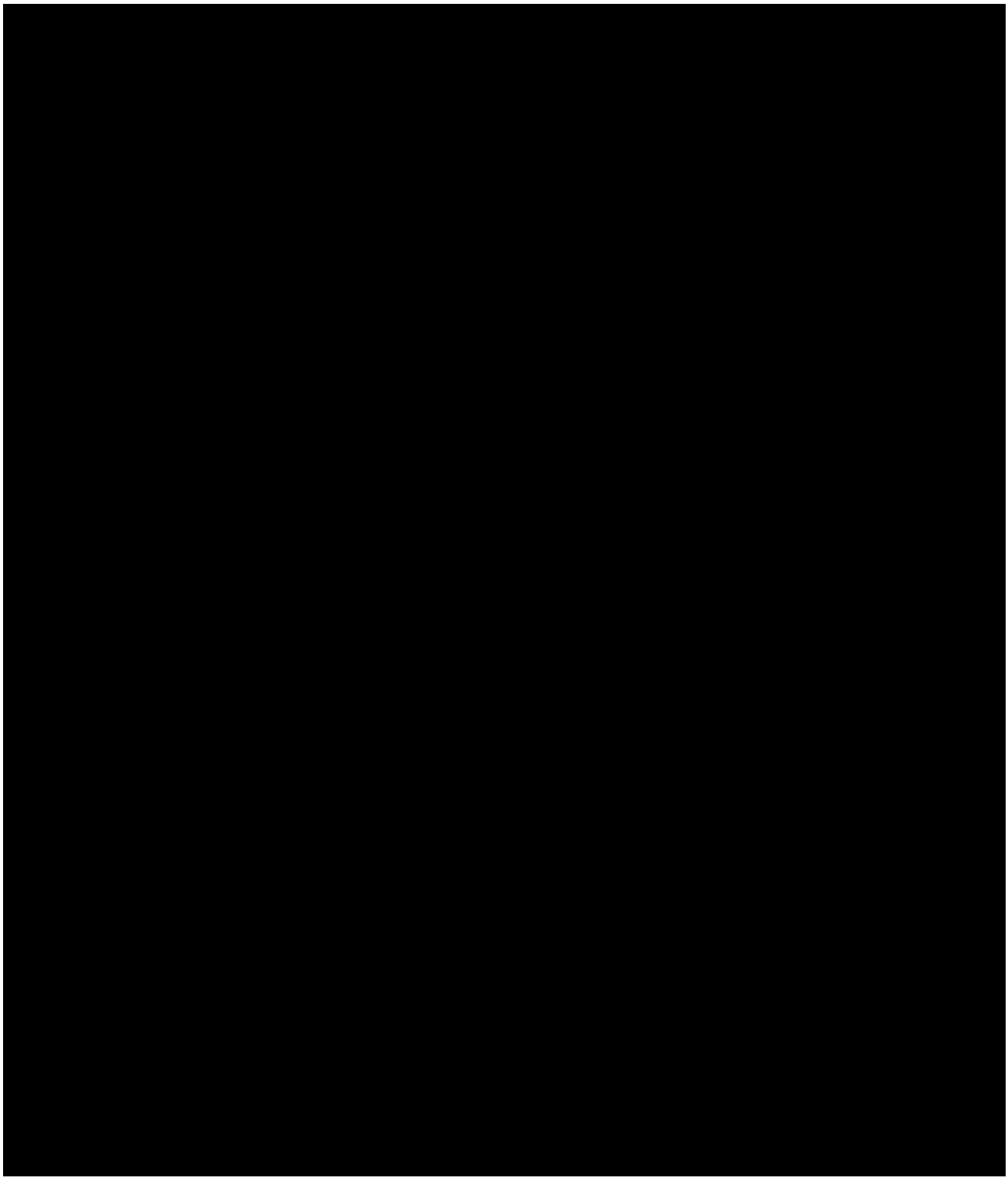

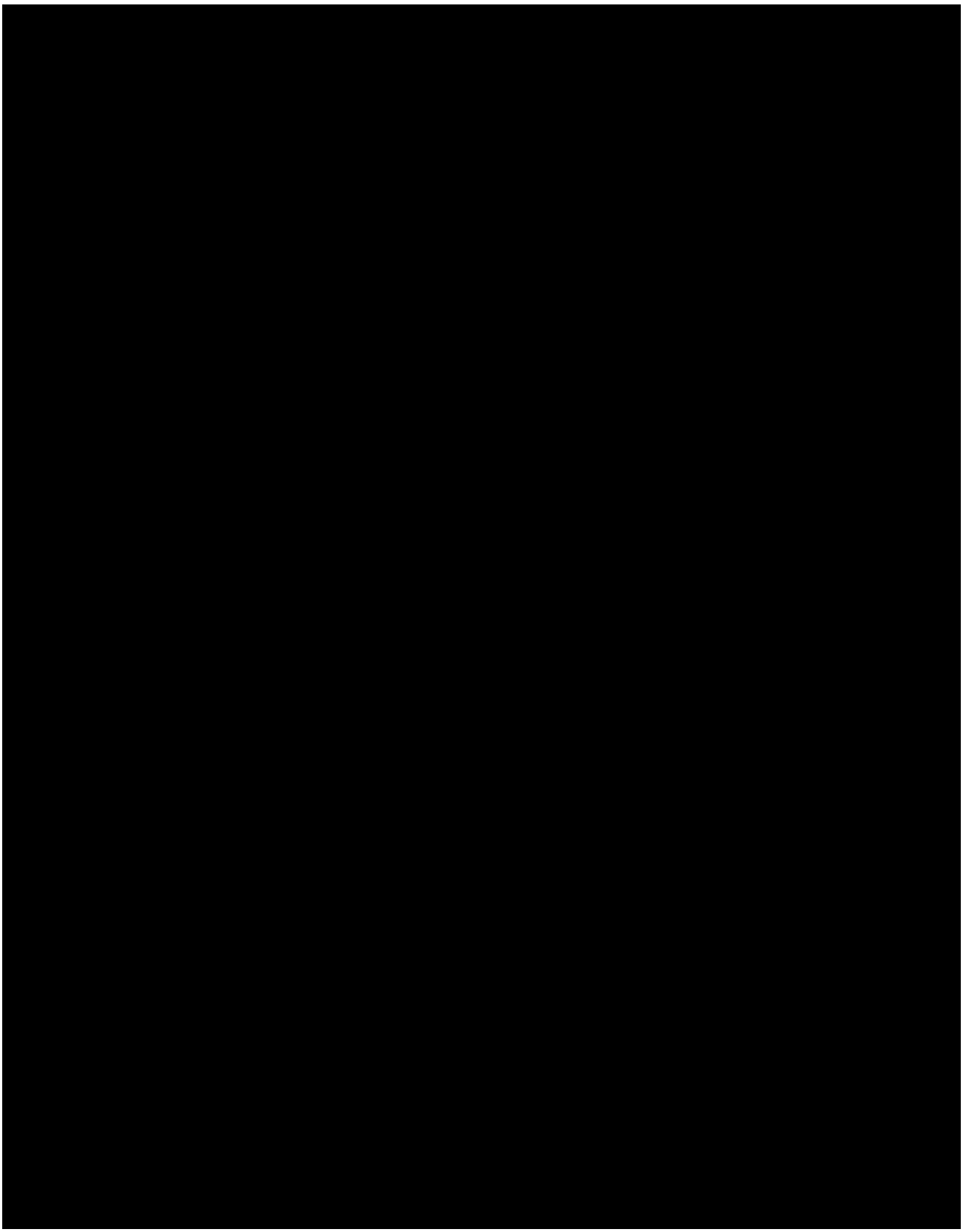

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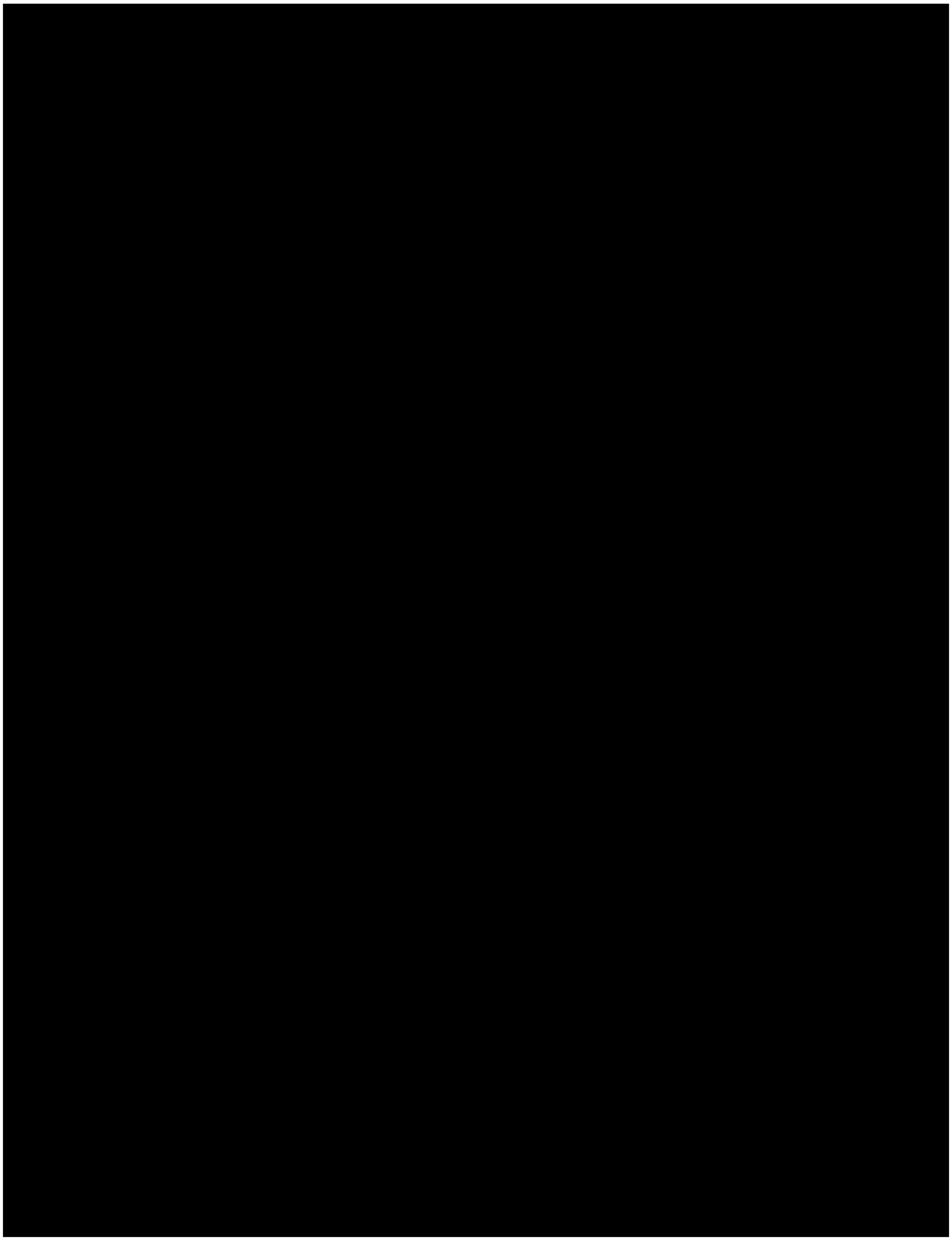

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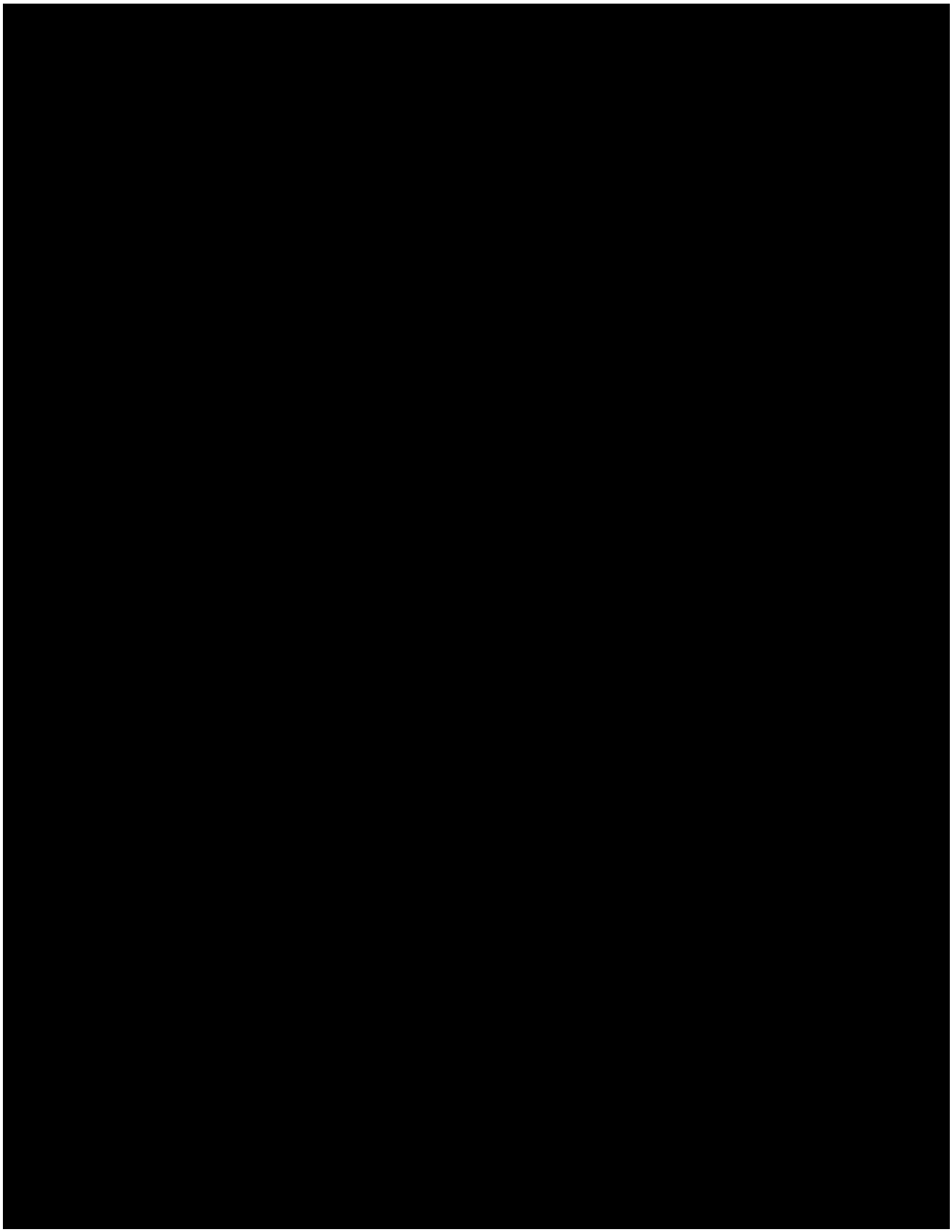

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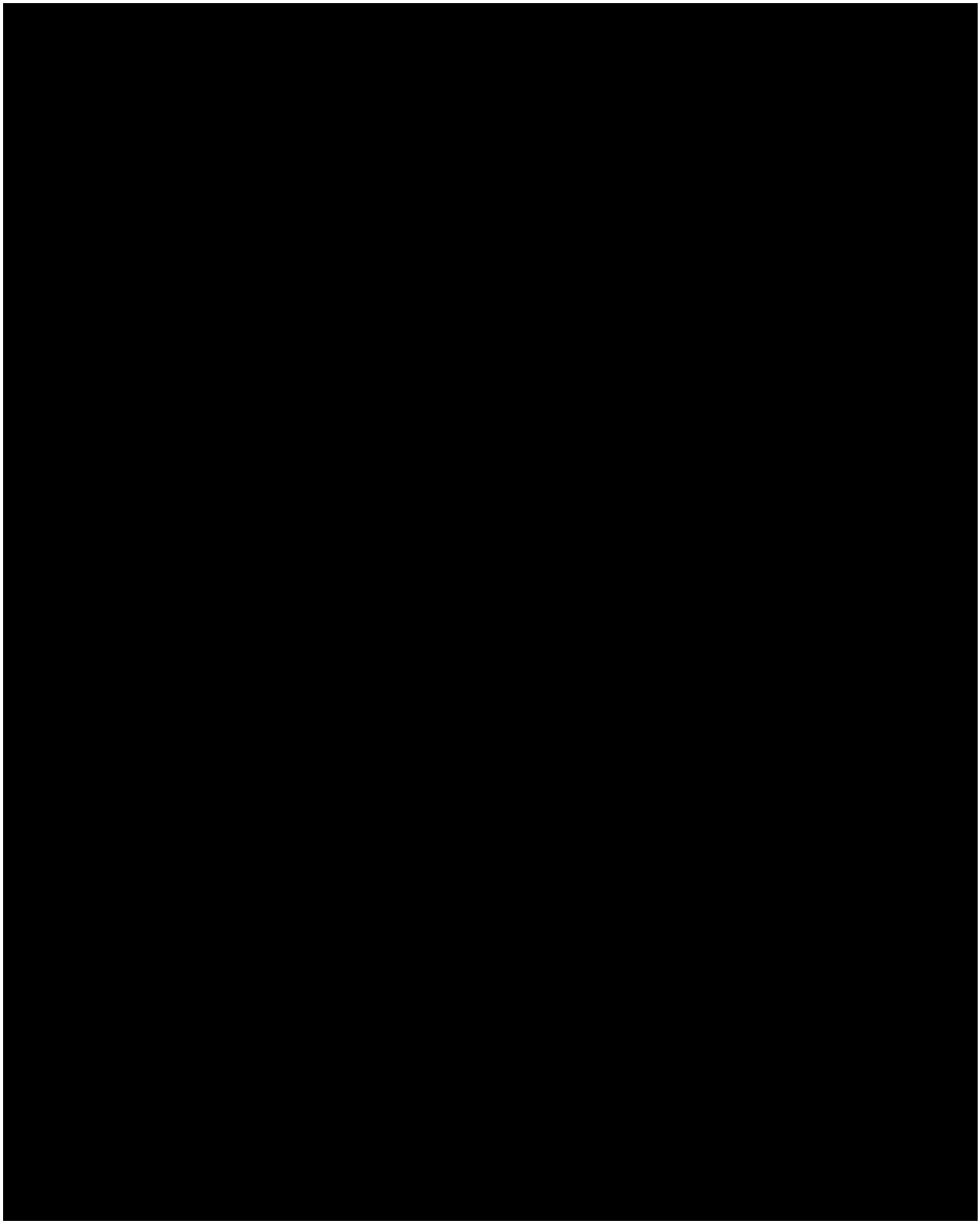

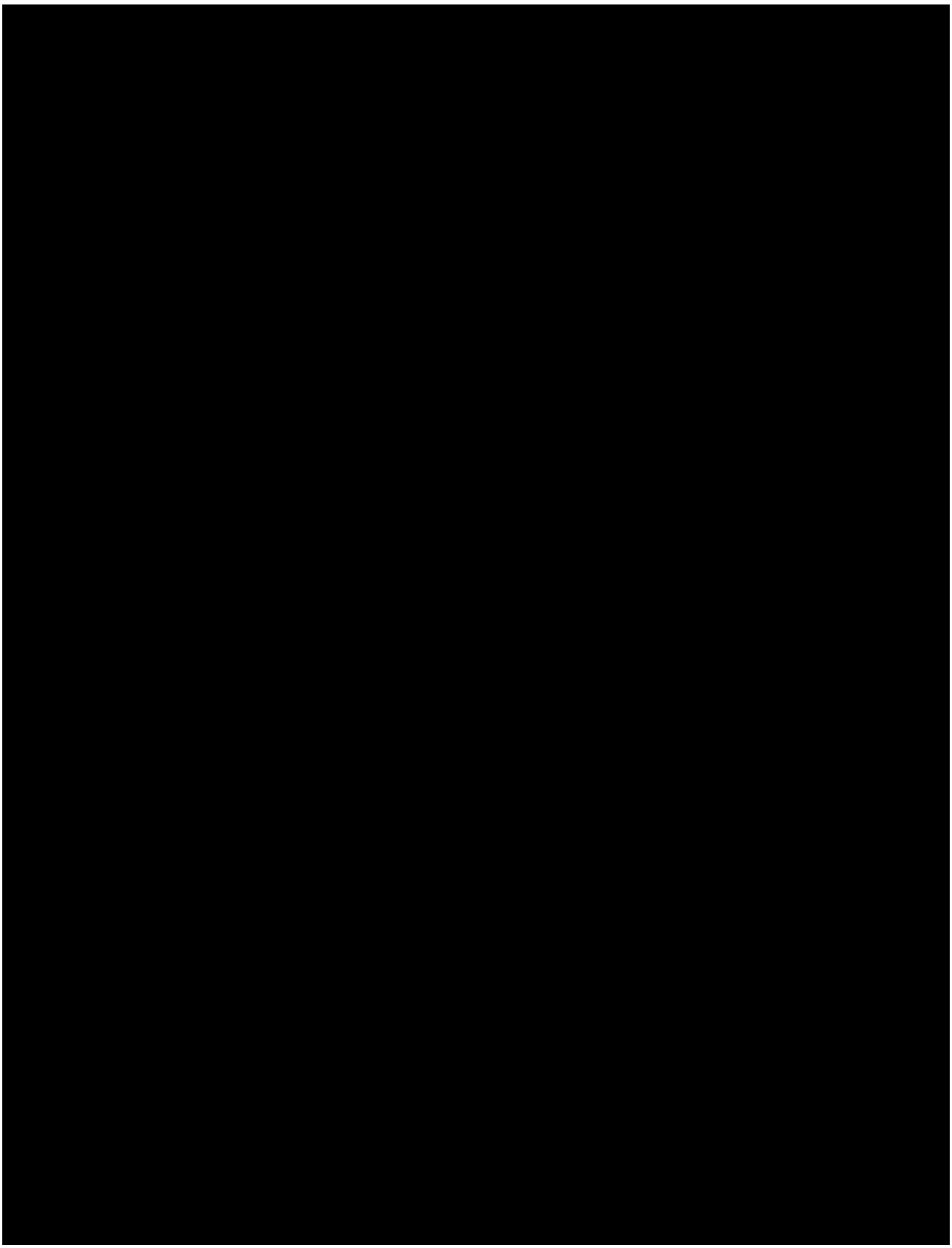

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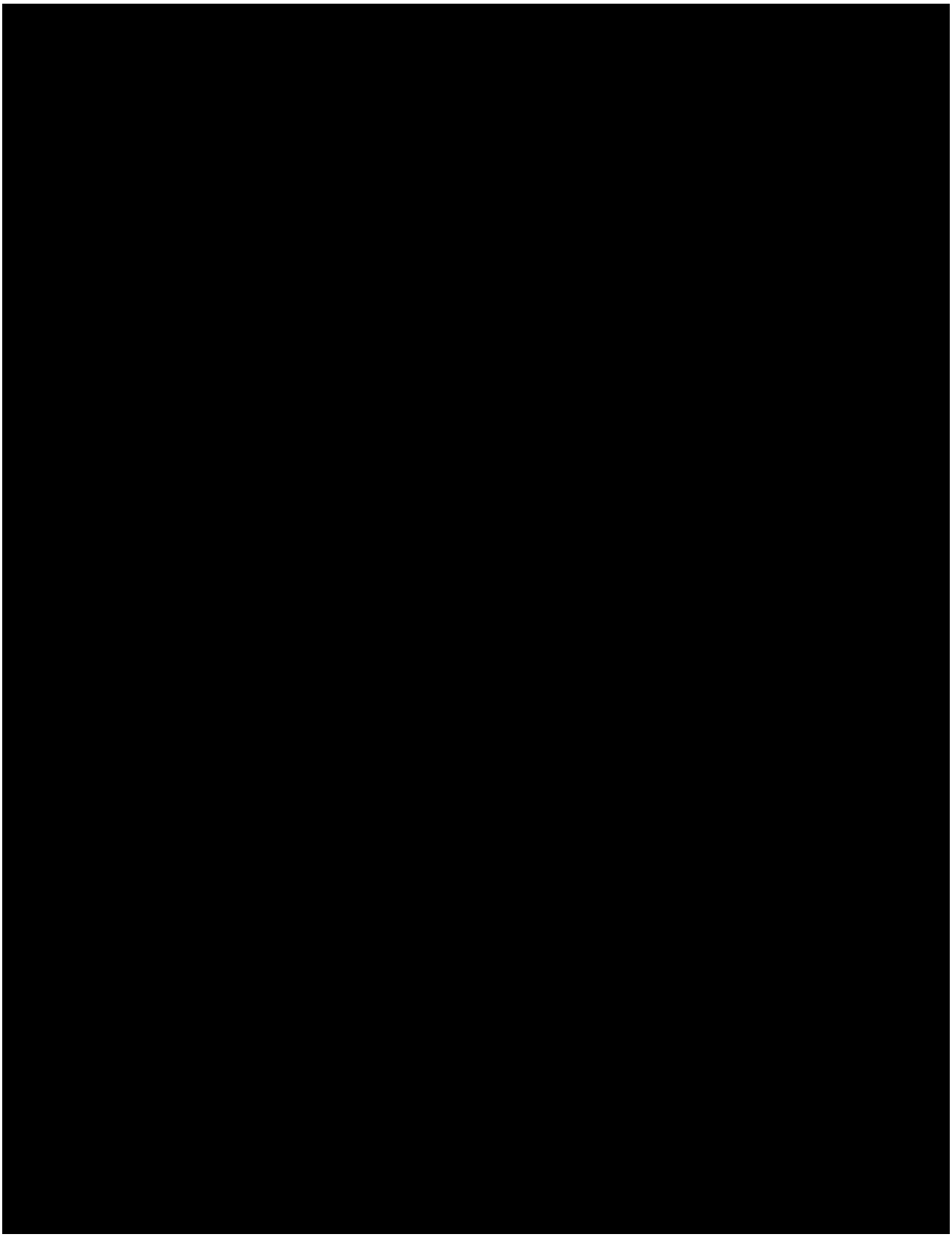

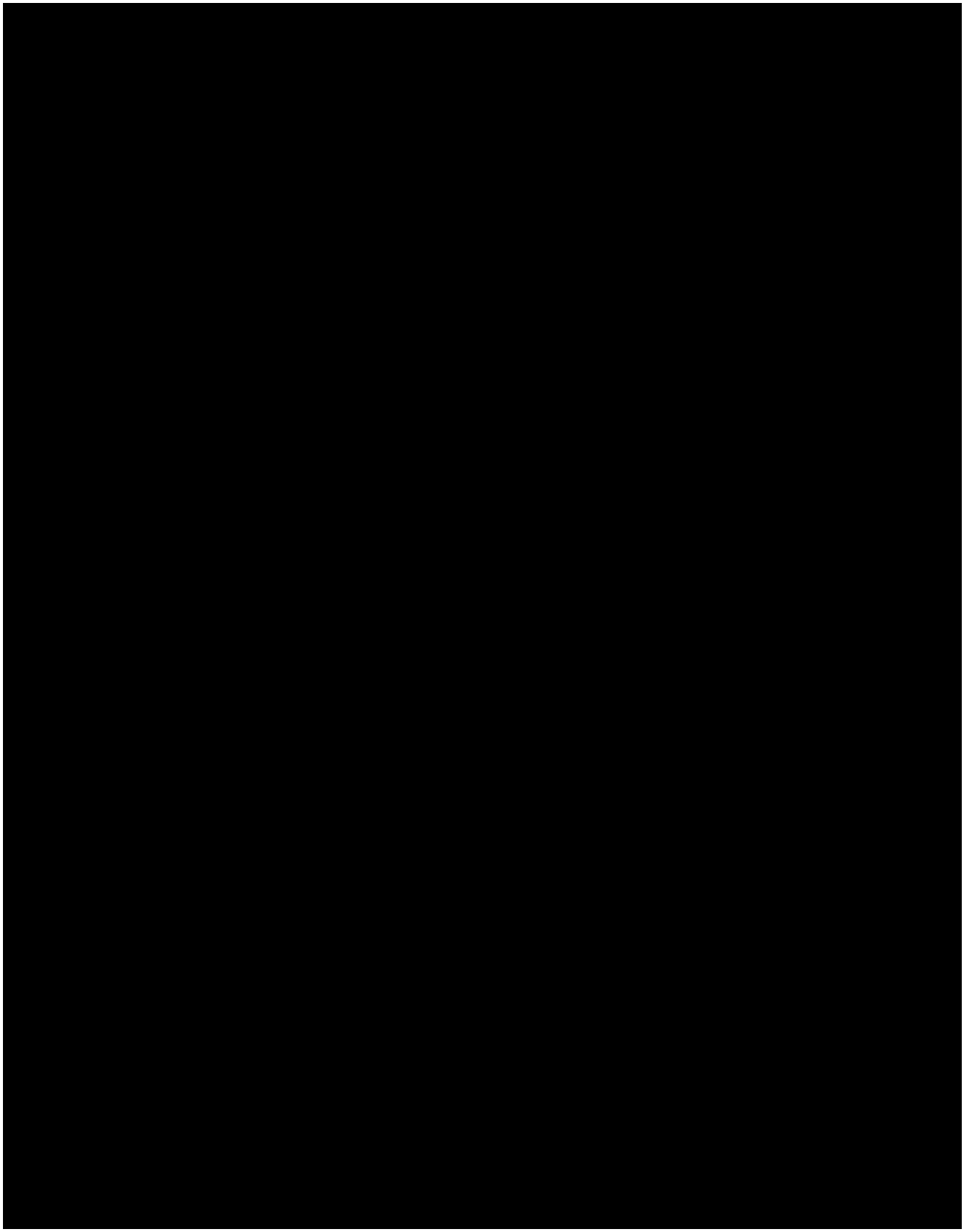

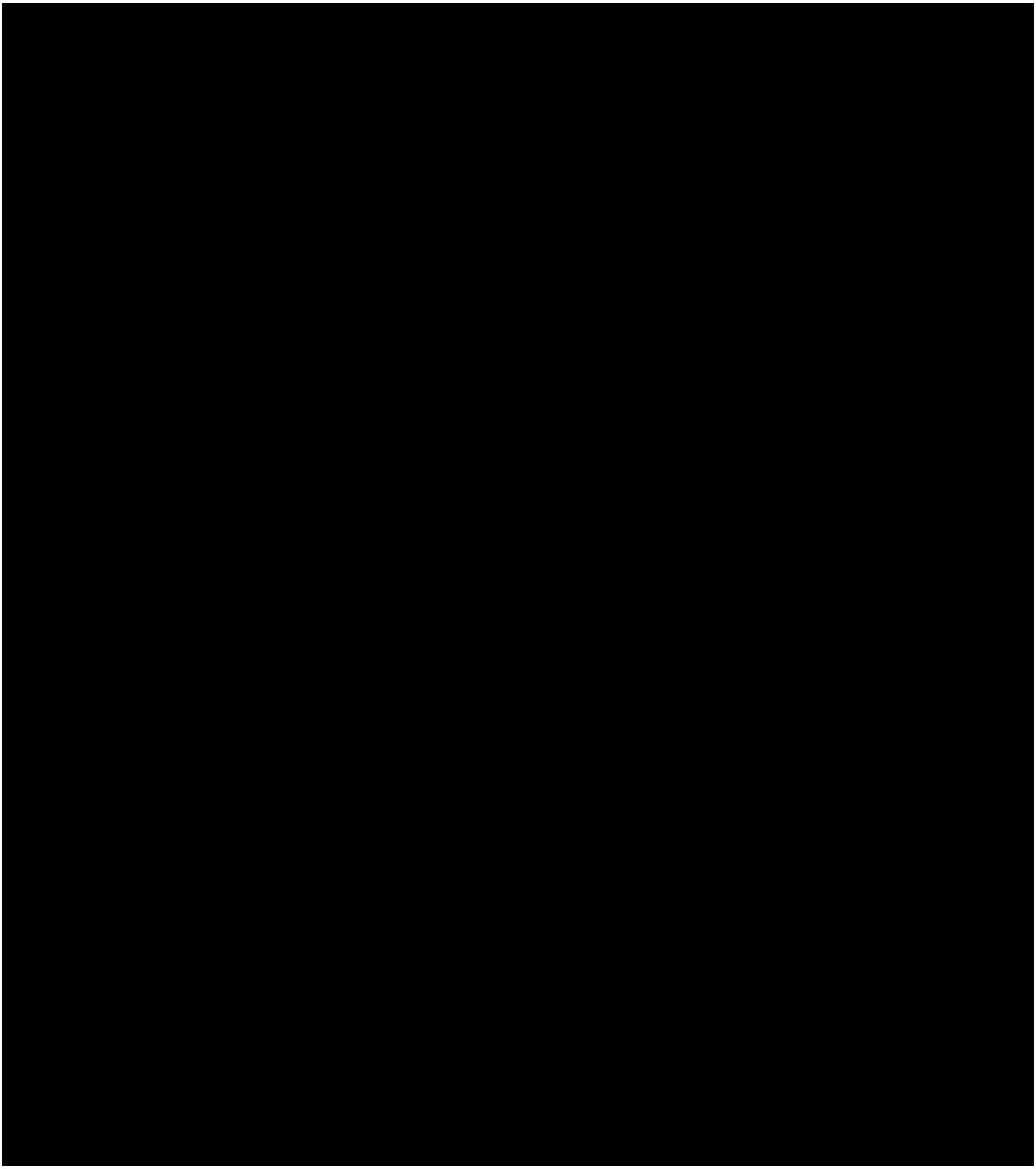

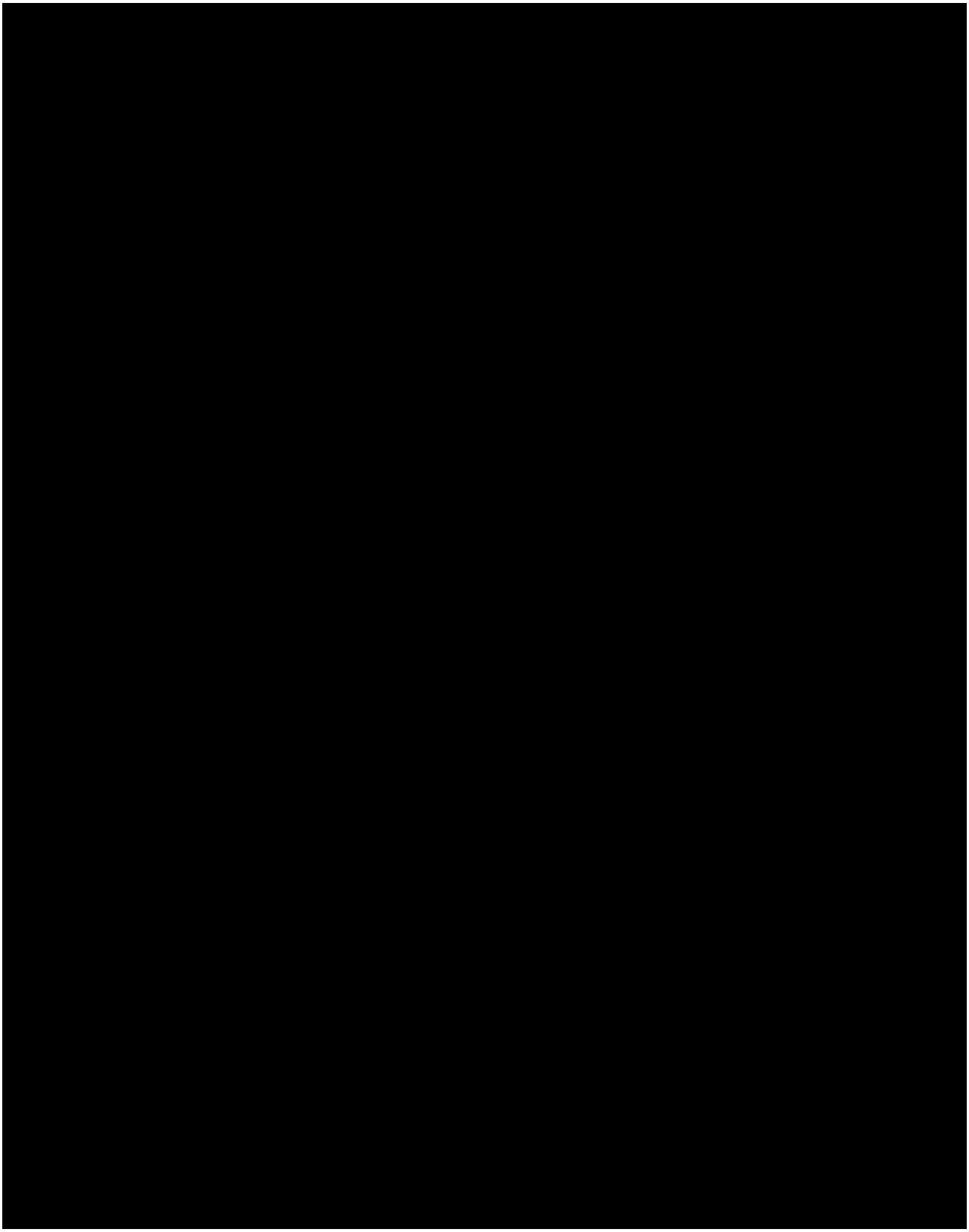

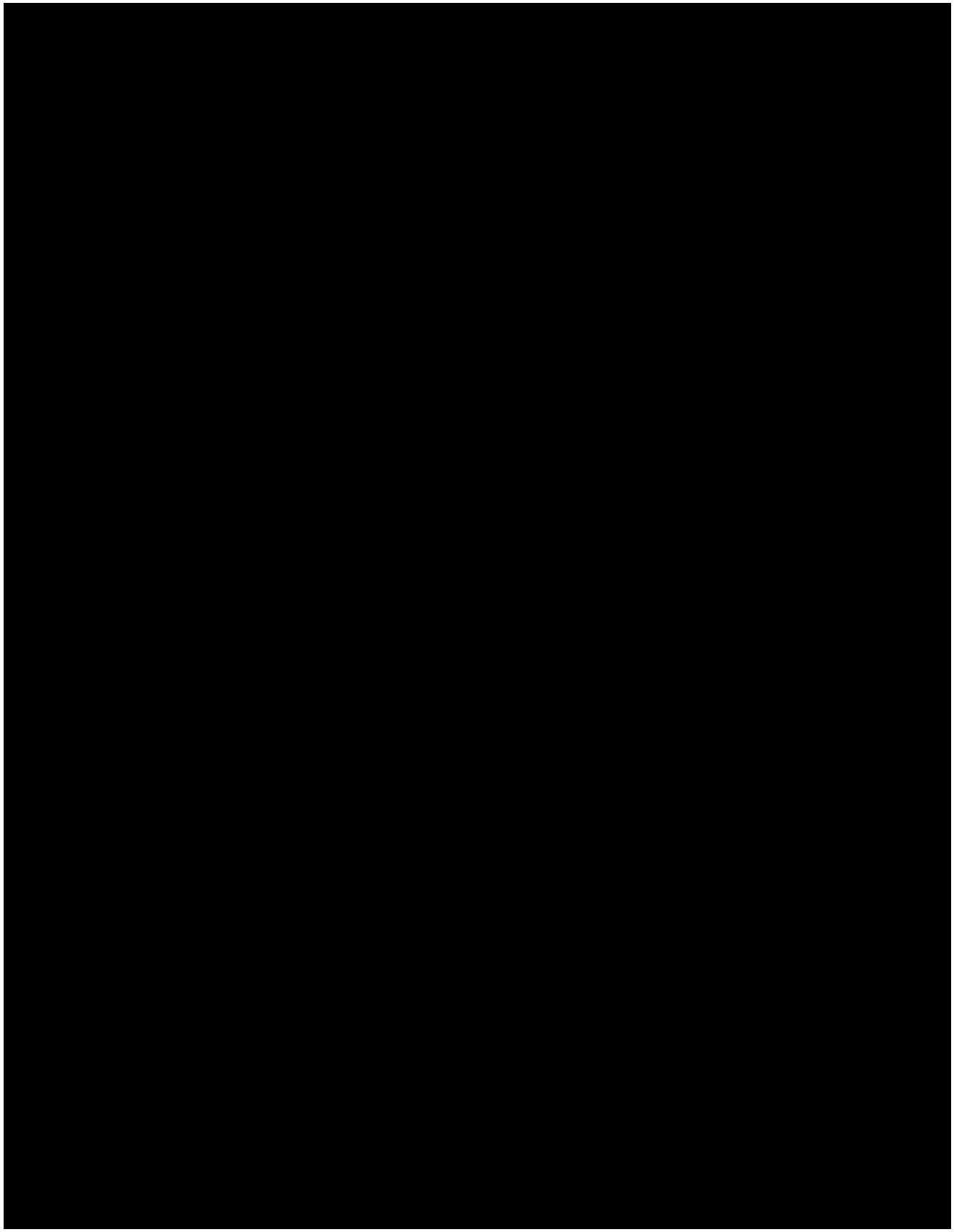

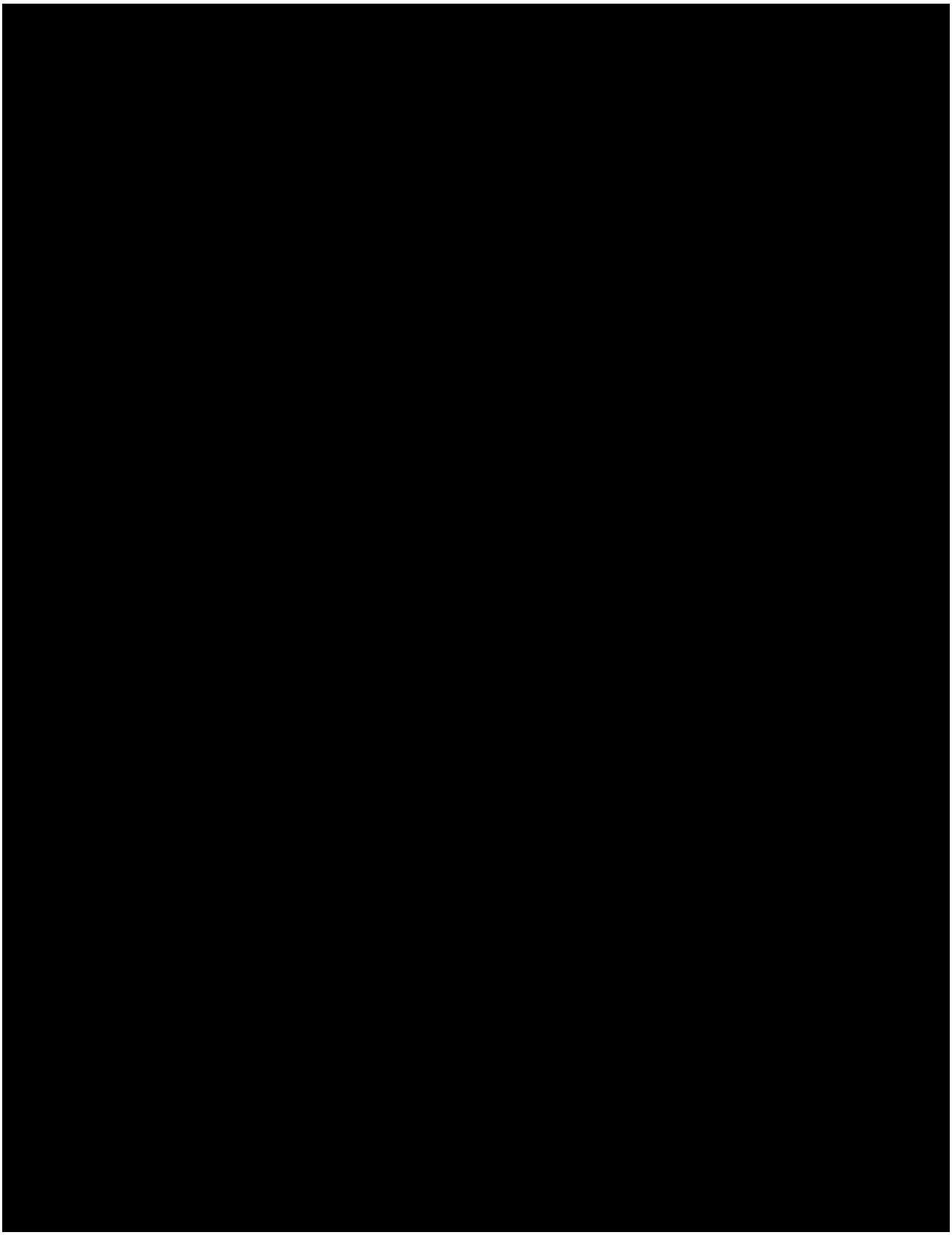

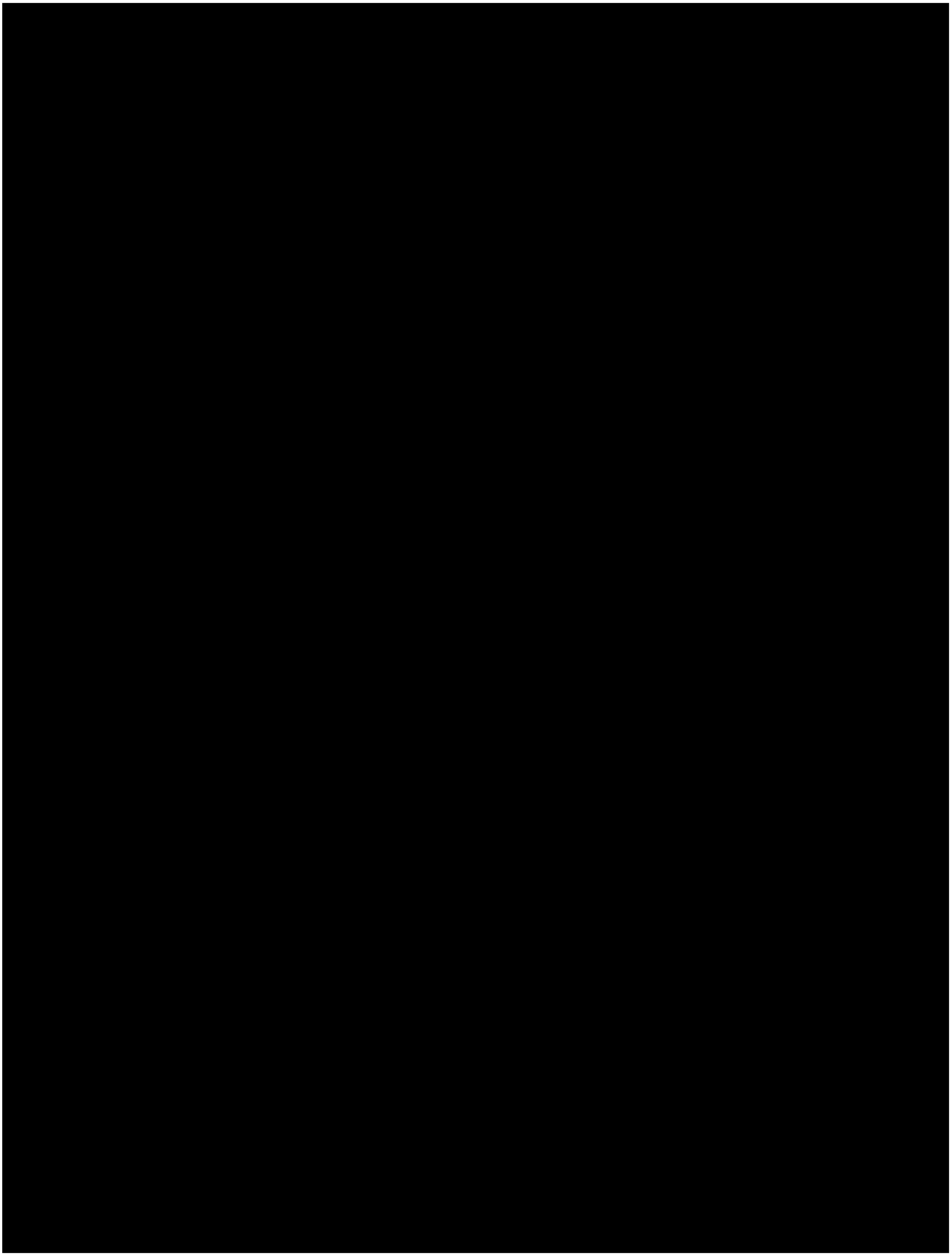

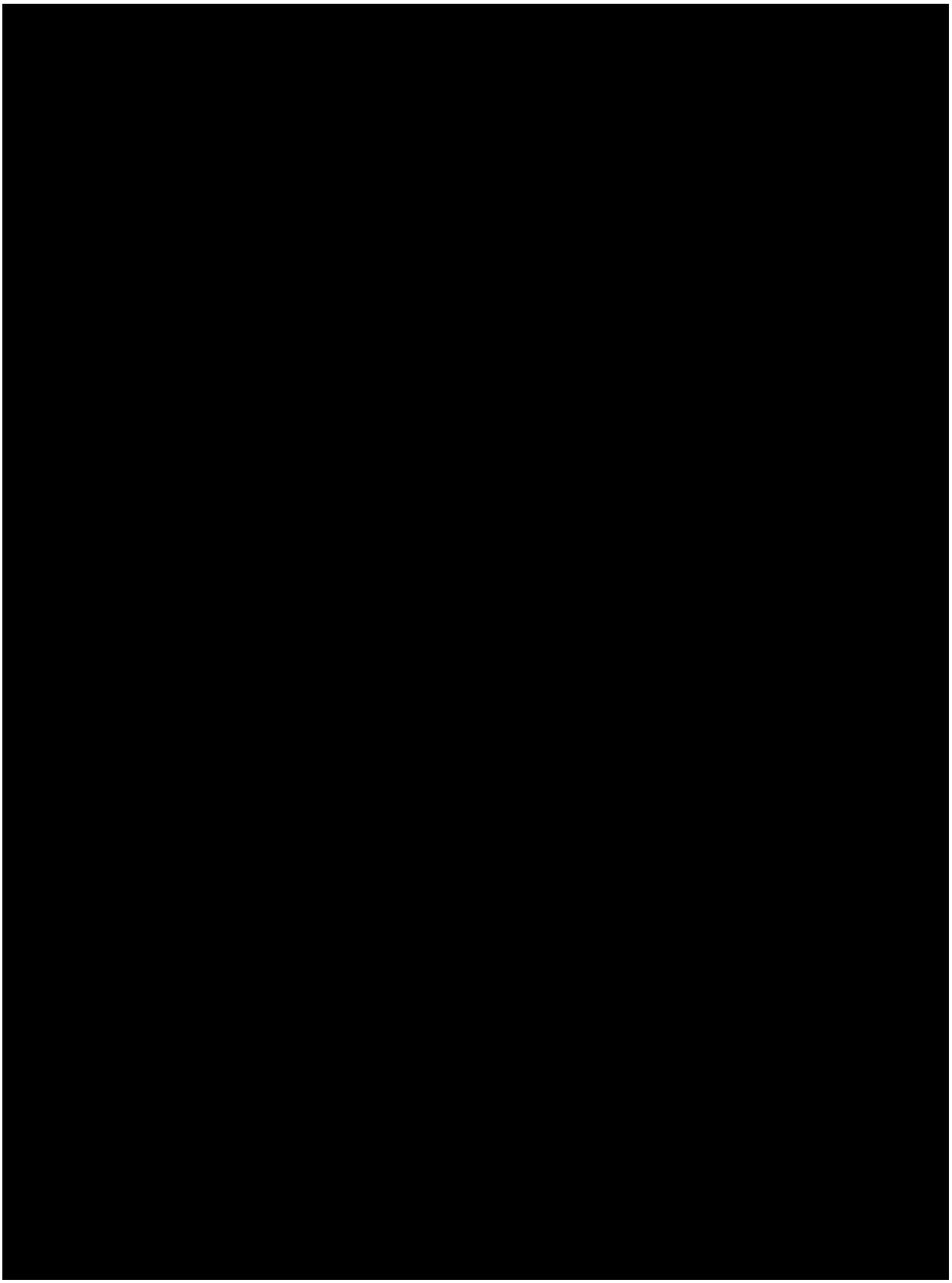

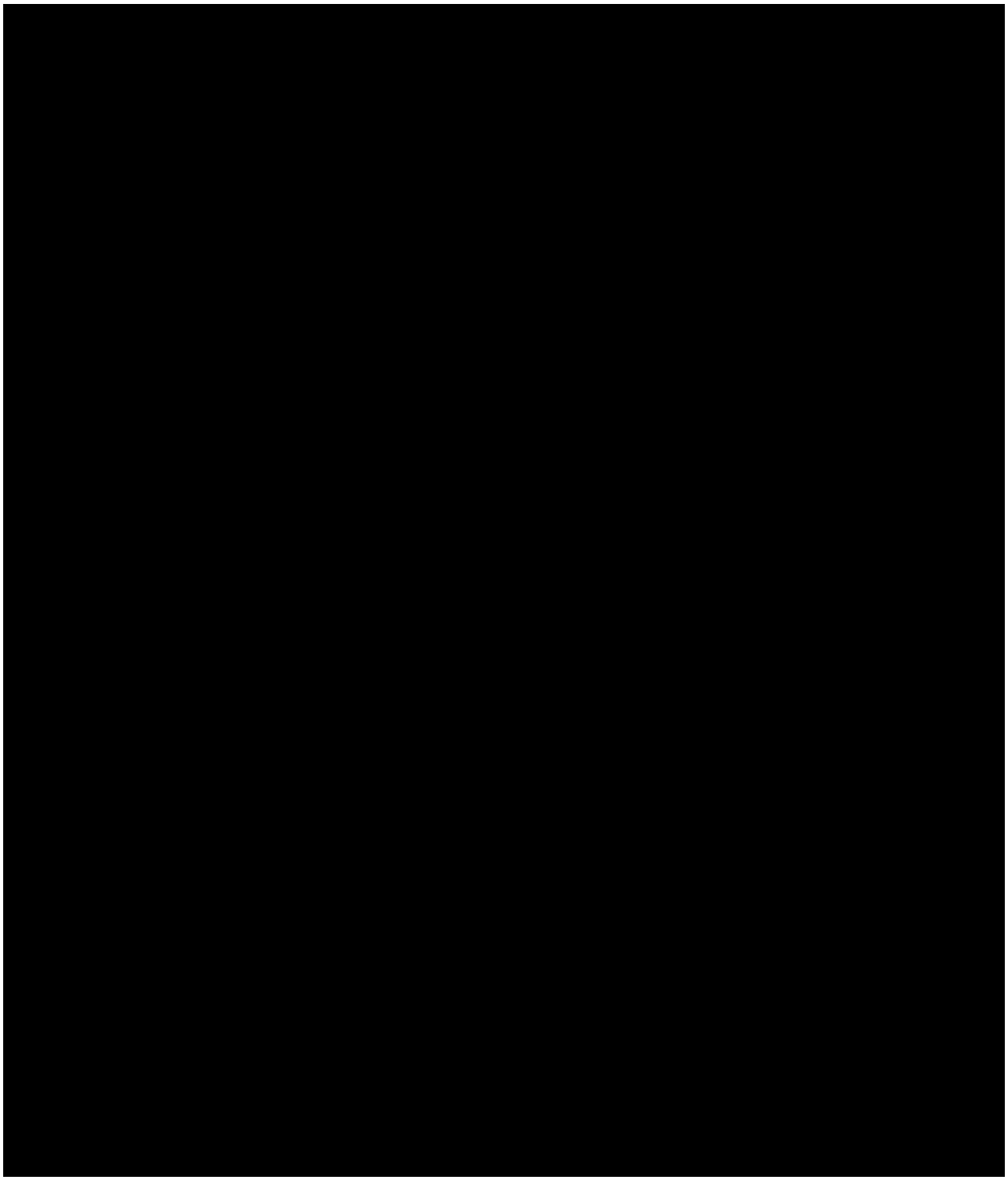

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