NOVARTIS

Clinical Development

LDE225 (Sonidegib) and INC424 (Ruxolitinib)

Oncology Clinical Protocol CLDE225X2116 / NCT01787552

A Phase Ib/II, open-label, multi-center, dose-finding study to assess the safety and efficacy of the oral combination of LDE225 and INC424 (Ruxolitinib) in patients with myelofibrosis

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List of abbreviations

µM	Micromolar
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
AML	Acute Myeloid Leukemia
ANC	Absolutely Neutrophil Count
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
AUC	Area under the concentration-time curve
AUC0-24h	Area under the concentration-time curve from zero up to 24 hours
AUC0-168h	Area under the concentration-time curve from zero up to 168 hours
AUClast	Area under the concentration-time curve from time zero to the time of last measurable concentration
AUCinf	Area under the concentration-time curve from time zero to infinity with extrapolation of the terminal phase
BAT	Best Available Therapy
BCC	Basal Cell Carcinoma
BCRP	Breast cancer resistance protein
BID	bis in diem/twice a day
BLRM	Bayesian Logistic Regression Model
BUN	Blood Urea Nitrogen
CDP	Clinical Development Plan
CK	Creatine Phosphokinase
Cmax	Maximum plasma concentration after administration
Cmin, Ctrough	Minimum (pre-dose) plasma concentration after administration
CML	Chronic myelogenous leukemia
CR	Complete Response
CRF	Case Report/Record Form; the term CRF can be applied to either EDC or Paper
CRO	Contract Research Organization
CSC	Cancer Stem Cell
CSR	Clinical study report
CSR addendum	An addendum to Clinical Study Report (CSR) that captures all the additional information that is not included in the CSR
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450 Genes
DDS	Dose Determining Set
DHH	Desert Hedgehog
DHEA	Dehydroepiandrosterone
DLT	Dose Limiting Toxicity
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report/Record Form
Emax	Maximum possible effect
EOT	End of treatment
ET	Essential Thrombocythemia
EU	European Union

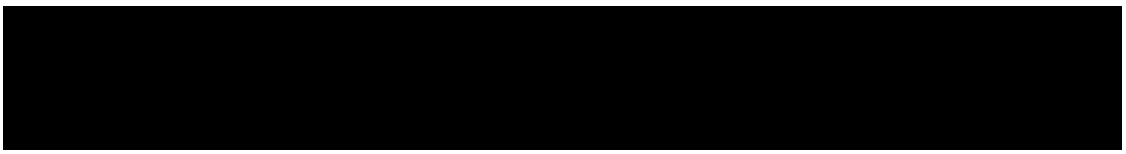
EWOC	Escalation with Overdose Control
FAS	Full Analysis Set
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
FSH	Follicle Stimulating Hormone
G	Grade
G-CSF	Granulocyte colony-stimulating factor
GI	Gastrointestinal
Gli	Glioma-associated oncogene homolog
GLP	Good Laboratory Practice
GPCR	G protein-coupled receptor-like
HEPM	Human embryonic palatal mesenchymal
Hh	Hedgehog
i.v.	intravenous(ly)
IC50	Half maximal inhibiting concentration
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IHH	Indian Hedgehog
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IUD	intrauterine device
JAK	Janus kinases
JAK1	Janus kinase 1
JAK2	Janus kinase 2
K_i	Inhibition constant
LFS	Leukemia-Free Survival
LMWH	Low Molecular Weight Heparin
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation
MB	Medulloblastoma
MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MPN	Myeloproliferative neoplasm
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic acid
MRP	Multi drug Resistance Protein
MTD	Maximum Tolerated Dose
NIH	National Institutes of Health
nM	Nanomolar
o.d.	omnia die/once a day
ORR	Overall Response Rate
OS	Overall Survival
PD	Pharmacodynamics
PD	disease progression
P-gp	P-glycoprotein
PHI	Protected Health Information
PK	Pharmacokinetics

[redacted]

PMF	Primary Myelofibrosis
PMR	partial metabolic response
PML	Progressive Multifocal Leukoencephalopathy
p.o.	per os/by mouth/orally
Post-PV MF	Post-polycythemia vera myelofibrosis
Post-ET MF	Post-essential thrombocythemia myelofibrosis
PR	Partial Response
PRO	Patient Reported Outcome
PT	Prothrombin time (PT)
PTCH	protein Patched
PTT	Partial thromboplastin time (PTT)
PV	Polycythemia vera
QC	Quality Control
QD	Once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
QoL	Qualiity of Life
RAP	The Report and Analysis Plan
RDC	Remote Data Capture
RDE	Recommended dose for expansion
REB	Research Ethics Board
RECIST	Response Evaluation Criteria in Solid Tumors
RMS	Rhabdomyosarcoma
RPIID	Recommended phase two dose
qRT-PCR	Quantitative reverse Transcriptase Polymerase Chain Reaction
RU	Resource Utilization
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SD	Stable Disease
sFRP1	secreted frizzled-related protein
SHH	Sonic Hedgehog
Smo	Smoothened
SOC	Standard of Care
SOP	Standard Operating Procedure
STAT	Signal transducer and activator of transcription
SuFu	Suppressor of fused
TK	Toxicokinetics
Tmax	Time to reach the highest concentration
TM3	Testicular Mouse (Leydig) cell line
ULN	Upper Limit of Normal
Vss	Volume of Distribution at steady state
WBC	White blood cell count

Glossary of terms

Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject or study patient
Cohort	A group of newly enrolled patients treated at a specific dose and regimen (i.e. treatment group) at the same time
Dose level	The dose of drug given to the patient (total daily or weekly etc.)
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Investigational drug	The study treatment whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drug whose properties are being tested in the study as well as their associated placebo and active treatment controls (when applicable). This also includes approved drugs used outside of their indication/approved dosage, or that are tested in a fixed combination. Investigational treatment generally does not include other study treatments administered as concomitant background therapy required or allowed by the protocol when used in within approved indication/dosage
Medication number	A unique identifier on the label of each study treatment package which is linked to one of the treatment groups of a study
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Subject Number (Subject No.)	A unique identifying number assigned to each patient/subject 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.
Stage related to study timeline	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study End / Study Completion	Point/time at which the patient came in for a final evaluation visit or when study treatment was discontinued whichever is later
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures
Study treatment discontinuation	Point/time when patient permanently stops taking study treatment for any reason
Treatment group	A treatment group defines the dose and regimen or the combination, and may consist of 1 or more cohorts. Cohorts are not expanded, new cohorts are enrolled.
Variable	Identifier 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



Amendment 2

Amendment rationale

As of 06 February 2015, 57 patients were screened, 50 patients treated (30 in the Phase Ib part and 20 in the Stage 1, Phase II part), and 7 patients were screen failures. Fourteen of the treated patients have discontinued treatment due to disease progression, adverse events, physician decision or patient decision. The RPIID was confirmed as the 400mg LDE225 QD + 20mg INC424 BID dose level. Patients enrolled in the Stage 1, Phase II part of the study are currently being observed for 24 weeks, and an interim analysis will occur at the end of the observation period.

The purpose of this protocol amendment is to add a treatment extension phase for patients who complete 2 years of study treatment and are deriving clinical benefit according to the investigator until other alternatives to receive study treatment from the sponsor become available. Currently no patients have completed 2 years of study treatment.

The amendment also includes other revisions and administrative changes for clarification purposes.

Changes to the protocol:

The following sections have been changed in the amended protocol:

Title page: Author list updated.

Glossary of terms updated.

Protocol summary updated

Section 1.4.1.2.1: Updated number of patients exposed to LDE225

Section 1.4.2: Updated INC424 indications to add PV; updated number of countries where INC424 is approved

Section 1.4.2.2: Updated number of patients exposed to INC424

Section 1.4.2.2.1: Updated the safety information for ruxolitinib per most recent IB

Figure 4-1 updated to reflect addition of extension phase

Section 4.1.1 and 4.3.1: Revised to include extension phase

Section 4.2.1: section removed since updated information is provided elsewhere

Section 4.3.2: Removed language for final data analysis at 1 year post LPFV treatment in Phase II

Section 6.1.5: Revised treatment discontinuation language to include extension phase

Section 6.2.1 Revised recommended phase II to maximum tolerated dose

Section 7.1: Revised Study Flow to add visit windows for extension phase and to add description for SOC; revised Table 7-1 to reflect addition of an extension phase and a Week

105 Day 1 visit to replace the previous EOT visit; added Table 7-2 to include visit evaluation schedule for extension phase

Section 7.1.2: Revised treatment period language to reflect addition of extension phase

Section 7.1.2.1: Section deleted

Section 7.1.3: Updated discontinuation of study treatment per DOCE

Section 7.1.4: Section added for Withdrawal of Consent per DOCE

Section 7.1.5: Follow up for safety evaluations language updated

Section7.1.6: Section added for Lost to follow up per DOCE

Section 7.2: Revised all subsections for assessments and sample collection time-points to reflect the addition of the extension phase visits as reflected in Table 7-2, which implements a reduction in scheduled visit assessments after Week 105

Table 7-3: Updated to reflect assessments in extension phase

Table 7-5: Updated to reflect assessments in extension phase; EOT biopsy sample not required if a prior sample was collected within 24 weeks, changed from 6 weeks, of EOT to reduce patient burden for this exploratory analysis

Section 7.2.2.5.6: Added required pregnancy testing in extension phase as monthly or more frequent per local regulations, with home testing kits provided

Section 7.2.3.1: Revised language for PK analytical method

Table 7-10: Biomarker samples previously collected at End of Treatment changed to Week 105 Day 1 or End of Treatment, whichever comes first)

Section 7.2.6.1.1 and Table 7-11: MFSAF collection plan revised to be collected every 12 weeks in extension phase

Section 7.2.6.1.2 and Table 7-11: EORTC QLQ-C30 MFSAF collection plan revised to be collected every 12 weeks in extension phase

Section 10: Modified to revise that final analysis will occur at end of study when all patients discontinue

Amendment 1

Amendment rationale

As of 06-Aug-2014, thirty six patients were screened, thirty patients treated, and six patients were screen failures in the Phase Ib part of the study. Five of the treated patients have discontinued treatment due to disease progression, adverse events, physician decision or patient decision. Out of nine patients in the Dose Determining Set at the 400mg LDE225 QD + 15mg INC424 BID dose level, two DLTs occurred during the 6 week (42 day) DLT observation period. The MTD was not reached and instead the RPIID was defined as the 400mg LDE225 QD + 20mg INC424 BID dose level. Patients enrolled in the Phase Ib safety

[redacted]

expansion cohort at 400mg LDE225 QD + 20mg INC424 BID are currently being observed in order to confirm the RPIID.

The major changes included in this amendment include: Addition of an exploratory endpoint to assess the levels of LDE225 in bone marrow, updates to the guidance for contraception based on a recent population pharmacokinetic analysis and updates to the muscle toxicity section for CK elevation.

[redacted]

Changes to contraception language

The recommendation for contraception duration has been updated based on a recent population pharmacokinetic analysis that showed a longer half-life of sonidegib in cancer patients (28 days) than in healthy subjects (10 days). Duration of pregnancy prevention was estimated via population pharmacokinetic model-based simulations incorporating the emerging data in cancer patients. The recommended duration of pregnancy prevention in female patients was extended from 6 months to 20 months to ensure the residual plasma sonidegib concentration is reduced below the safety threshold of 3pg/mL. The recommended condom use for 6 months for male patients with partners of child-bearing potential did not change as the 6-month duration is considered adequate to minimize any risk of sonidegib being transmitted to female partners via the seminal fluid of male patients. Female patients of child-bearing potential who had discontinued sonidegib before the current protocol amendment were informed of the need for extended contraception for 20 months.

[redacted]

Changes to the protocol:

The following sections have been changed in the amended protocol:

[redacted]

Changes to the title page:

- The LDE225 International Nonproprietary Name (INN), sonidegib, added.
- Author list updated.

List of abbreviations updated.

Glossary of terms updated.

Protocol summary (Purpose and rationale): Updated number of countries INC424 is approved in.

Protocol summary (Exclusion criteria): revised aspirin dose to 150mg/day to be consistent with other INC424 studies.

Protocol summary (Other assessments): Inserted 'Bone marrow aspirate samples for pharmacokinetic and pharmacodynamic analysis.

Section 1.4.1.2.1: Updated the total number of subjects, including patients that were dosed with LDE225 as of the most recent Investigator Brochure.

Section 1.4.1.2.3: Updated information from a food effect study. 'In study [CLDE225A2114] in healthy volunteers with a 12-week follow-up period after a single dose, the geometric mean terminal half-life is estimated to be 10 days with a range of 3-32 days. In addition, a high-fat meal increased the C_{max} and AUC of LDE225 capsules compared with the fasting condition. In anticipation of a food effect, food consumption will continue to be restricted around the time of dosing in clinical studies.'

Section 1.4.1.2.3 – Inserted language based on an update from a recent population pharmacokinetic analysis.

Section 1.4.2: Updated number of countries INC424 is approved in.

Section 1.4.2.2: Updated the total number of subjects and patients that were dosed with INC424 as of the most recent Investigator Brochure.

Section 1.4.2.2.1: Updated data for tuberculosis reports.

Section 1.4.2.2.1: Added PML (Progressive Multifocal Leukoencephalopathy) language.

Section 3: Table 3-1, added a new Phase II exploratory objective 'To assess the levels of LDE225 in bone marrow'

Section 4.1: Figure 4-1, Clarified in the study schema that the Phase Ib part of the study is comprised of an escalation and safety expansion stage. Also included mention of the roll-over study.

Section 4.1.1: Added bone marrow aspirate sample collection for LDE225 concentration measurement.

Section 4.1.2: Updated section to be consistent with the LDE225 program roll-over study language.

Section 5.1: Sentence updated to indicate that only JAK inhibitor naïve patients are allowed into the study to be consistent with the rest of the document.

[redacted]

Section 5.3: Exclusion criteria #7, revised allowable aspirin dose level to 150mg/day to be consistent with other INC424 studies.

Section 5.3: Exclusion criteria #16: The time period for which women of child-bearing potential must use highly effective contraception after the final dose of study treatment was increased from 6 to 20 months.

Section 5.3: Exclusion criteria #16: Clarified that male patients should use contraception and refrain from fathering a child for 6 months following the last dose of study drug.

Section 6.2.5: Table 6-3, updated the toxicity classification for liver function DLTs to "Hepatic".

[redacted]

Section 6.4.3.4: Reworded this section for greater clarity.

Section 6.5.1: Removed reference to patient numbering in the setting of re-screening since re-screening is not allowed in the study.

Section 7.1: Clarified that baseline (Week 1 Day 1) abdominal imaging (MRI/CT) and bone marrow samples must be performed before study medication is taken:

- Added the allowable window for baseline abdominal imaging (MRI/CT) as - 1 week.
- Added the allowable window for baseline bone marrow biopsy and aspirate sample collection as - 2 weeks.

[redacted]

Section 7.1: Table 7-1, clarified that serum and urine pregnancy testing should only be performed in women of child bearing potential to be consistent with other studies in the LDE225 program, there is no safety risk to women who do not meet this criteria.

[redacted]

Section 7.1.2: Roll-over protocol language added.

Section 7.2.1.3: Removed collection of bone marrow samples at Week 13, this was an error in the original protocol text.

[redacted]

Section 7.2.2.5: Table 7-5, Added "Urinalysis" label to the relevant group of analytes.

[redacted]

[redacted]

Updated Section 7.2.2.5.6: Clarified that local serum and urine pregnancy testing is only required for women of child-bearing potential to be consistent with other studies in the LDE225 program, there is no safety risk to women who do not meet this criterion.

[redacted]

Section 9.3: Removed EMG and muscle biopsy.

Section 9.4: Removed EMG and muscle biopsy.

Section 10.2: Deleted '25th and 75th percentiles.'

Section 10.3.1: Deleted 'Data may be presented by week in addition to over the entire treatment duration.'

Section 10.3.2: Clarified concomitant medications summaries will be based on full analysis set instead of safety set.

Section 10.5.1.1: Clarified the language used for deaths and SAEs.

Section 10.5.1.2: Deleted 'Classification to compare baseline to the worst on treatment value' as this analysis is covered in the shift table.

[redacted]

Section 10.7: Table 10-6, Updated to be consistent with the Beta prior.

Section 10.7: Deleted 'independent statistician' for 'the number of responders needed will be determined at the time of interim analysis' since this is an open label, un-blinded study.

Section 10.7: Deleted 'and a prior sample size of less than 8 patients' for greater clarity.

[redacted]

IRB/IEC/REB Approval

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

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

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

[redacted]

Protocol summary

Protocol number	CLDE225X2116
Title	A Phase Ib/II, open-label, multi-center, dose-finding study to assess the safety and efficacy of the oral combination of LDE225 and INC424 (Ruxolitinib) in patients with Myelofibrosis
Brief title	A study to find the maximum tolerated dose and determine the efficacy of the experimental combination of LDE225 and INC424 in patients with Myelofibrosis
Sponsor and Clinical Phase	Novartis Ib/II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this phase Ib/II clinical trial is to: a) evaluate the safety of the co-administration of LDE225 and INC424 in myelofibrosis patients and establish a maximum tolerated dose and/or Recommended Phase II dose of the combination and b) to assess the efficacy of the co-administration of LDE225 and INC424 on spleen volume reduction. INC424 has shown efficacy in myelofibrosis (MF) and is approved in over 50 countries. LDE225 is a Hh pathway inhibitor. Pre-clinical data showed an encouraging effect of the combination on disease burden measurements, such as WBC count, spleen and liver weight. LDE might also demonstrate disease-modifying effects via reduction in bone marrow fibrosis and inhibition of cancer-initiating cells. Combining LDE225 and INC424 could therefore potentially provide improved clinical benefit to MF patients.
Primary Objective(s) and Key Secondary Objective	Phase Ib: establish the MTD and/or RPIID of the combination of LDE225 (QD) and INC424 (BID) when administered orally to patients with MF who have not previously received therapy with JAK and Smo inhibitors. Phase II: assess the efficacy of the co-administration of LDE225 and INC424 on spleen volume reduction as determined by centrally reviewed MRI/CT.
Secondary Objectives	Phase Ib: To evaluate the safety of the co-administration of LDE225 and INC424 in patients with MF. To characterize the single and multiple dose pharmacokinetics following the co-administration of LDE225 and INC424. Phase II: To assess the effect of the co-administration of LDE225 and INC424 on bone marrow fibrosis by central review and on disease-specific pharmacodynamic biomarkers as a function of the molecular disease characterization of MF. To evaluate the safety of the co-administration of LDE225 and INC424 in patients with MF. To characterize the single and multiple dose pharmacokinetics following the co-administration of LDE225 and INC424. To assess the effect of the co-administration of LDE225 and INC424 on MF-associated symptoms burden.

[redacted]

Study design	This is a multi-center, open-label, dose-finding phase Ib/II study to evaluate the safety and efficacy of the co-administration of LDE225 and INC424 in patients with Myelofibrosis (MF) who have not been previously treated with JAK and Smo inhibitors. Patients will undergo a screening phase. Once eligibility (screening criteria met) has been confirmed patients will be enrolled to either the Phase Ib or Phase II part of the study. Phase Ib: Groups of 3-6 patients will be enrolled into cohorts of increasing doses of LDE225 and INC424 until an MTD/RPIID is defined. If thrombocytopenia related dose limiting toxicities (DLTs) are observed during the dose escalation part of the study, different recommended dose combinations for patients with low and high baseline platelet counts may be suggested, in which case two MTDs/RPIIDs will be declared. Six additional confirmatory patients will be enrolled at each MTD/RPIID. Phase II: Patients will receive the dose(s) declared as the MTD/RPIID(s). Approximately 18 patients will be enrolled into Stage 1, if following an interim analysis the minimum number of responders are observed, 28 additional patients will be enrolled into stage 2. Patients will continue study treatment for at least 2 years after the first dose or until death, documented disease progression, initiation of a new MF therapy, intolerable toxicity, withdrawal of consent, discontinuation at the discretion of the investigator, or lost to follow-up, whichever comes first. Spleen volume assessments will be performed at Week 1, 13, 25 and 49 for Phase Ib patients enrolled to the confirmatory MTD level(s) and all patients enrolled in the Phase II part. Patients who complete 2 years of treatment and are deriving clinical benefit in the opinion of the investigator will be allowed to continue receiving treatment (LDE225 and INC424) in an extension phase of this study, until discontinuation reasons are met or an alternative setting to receive study treatment (e.g., in form of another protocol) becomes available. After discontinuing the study treatment, the patient will undergo an End Of Treatment visit as soon as possible and a 30-day safety follow-up evaluation. Imaging data will be centrally collected and checked for quality by a vendor designated by Novartis, but the decision regarding patient management will remain with the local investigator. A Steering Committee will be established and will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require.
Population	Adult patients, aged ≥ 18 years, with primary or secondary myelofibrosis that meet intermediate or high risk prognostic criteria and exhibit palpable splenomegaly ≥ 5 cm below the left costal margin that have not been previously treated with a JAK or Smo inhibitor will be eligible for this study. Approximately 36 patients will participate in the Phase Ib dose escalation and safety expansion part of the study. In the Phase II part of the study approximately 46 patients will be enrolled: 18 patients will be enrolled into Stage 1, if following an interim analysis at least 8 responders (i.e., patients with a spleen volumetric reduction from baseline of at least 35% by MRI/CT at 24 weeks) are observed, 28 additional patients will be enrolled into stage 2. If less than 8 responders are observed in Stage 1 then further enrollment will be halted for futility. Accounting for patients that may withdraw from the study or who may not meet the eligibility criteria, it is expected that approximately 82 patients will be enrolled in the entire study.
Inclusion criteria	Patient must be diagnosed with PMF per 2008 WHO criteria, or post-PV MF or post-ET MF per IWG-MRT criteria. Patient is ineligible or unwilling to undergo stem cell transplantation. Patient has a platelet count ≥ 75 x 10^9/L not reached with the aid of transfusions. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 at Screening. Patient must have palpable splenomegaly defined as ≥ 5 cm below the left costal margin. Patient must be classified as intermediate risk level 1 (1 prognostic factor which is not age), Intermediate risk level 2, or high risk per IWG criteria. Patient must have active symptoms of MF as demonstrated by one symptom score of at least 5 (0 to10 point scale) or two symptom scores of at least 3 (0 to 10 point scale) on the MF Symptom Assessment Form (MFSAF) at Screening.

[redacted]

Exclusion criteria	Previous therapy with JAK inhibitors. Previous therapy with a Smoothened inhibitor. Patient has impaired cardiac function or clinically significant heart disease. Patient is currently on medications that interfere with coagulation (including warfarin) or platelet function. Low dose aspirin (up to 150 mg per day) and low molecular weight heparin (LMWH) are allowed. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of INC424 or LDE225 (e.g., uncontrolled nausea, vomiting, diarrhea; malabsorption syndrome; small bowel resection). Patient had splenic irradiation within 12 months prior to Screening. Patients who have neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or are on concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins), clofibrate and gemfibrozil. Pravastatin may be used if necessary, with extra caution. Patients who plan on embarking on new (or unaccustomed) physical activities, such as strenuous exercise, that can result in significant increases in blood CK levels while on study treatment. NOTE: As a precaution, strenuous muscular activity should be avoided for at least 1 week prior to testing for blood CK levels. Patients receiving treatment with medications known to be moderate and strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting treatment with LDE225. Medications that are strong CYP3A4/5 inhibitors should be discontinued at least 7 days and strong CYP3A/5 inducers for at least 2 weeks prior to starting treatment with LDE225.
Investigational and reference therapy	Phase Ib: INC424 and LDE225 will be administered in increasing doses to cohorts of approximately 3-6 patients as follows: Dose level (1): INC424 10 mg BID, LDE225 400mg QD Dose level (2): INC424 15 mg BID, LDE225 400mg QD Dose level (3): INC424 15 mg BID, LDE225 800mg QD Dose level (4): INC424 20 mg BID, LDE225 800mg QD These doses may be adjusted following the recommendation of an adaptive BLRM for dose escalation with overdose control (EWOC) until an MTD/RPIID is defined. If thrombocytopenia related dose limiting toxicities (DLTs) are observed during the dose escalation part of the study, different recommended dose combinations for patients with low and high baseline platelet counts may be suggested, in which case two MTDs/RPIIDs will be declared. Six additional confirmatory patients will be enrolled at each MTD/RPIID. Phase II: Patients will receive the dose(s) declared as the MTD/RPIID(s).
Efficacy assessments	Measurement of palpable spleen length. Spleen volume reduction measured by MRI/CT. Bone marrow assessments (fibrosis and histomorphology). PRO assessment of MF-related symptoms, inactivity, functioning, overall QOL and assessment of improvement using the Seven-day Modified MFSAF v2.0 and EORTC QLQ-C30 questionnaires.
Safety assessments	Monitor the frequency, duration and severity of dose limiting toxicities, adverse events and serious adverse events, vital signs, physical exam and lab test abnormalities. Cardiac safety assessment: ECG.
Other assessments	PK assessments to characterize the pharmacokinetics of INC424 alone and in combination with LDE225, as well as at varying doses of the combination. Bone marrow aspirate samples for pharmacokinetic and pharmacodynamic analysis. [redacted] Analysis of JAK mutation status and allele burden, Hh pathway activation, cytokine assays and pharmacogenomics to explore potential predictive biomarkers and changes in markers of disease burden and symptoms.

[redacted]

Data analysis	Phase Ib: A 6-parameter Bayesian Logistic Regression Model (BLRM) for combination treatment will be fitted to the 6-week dose-limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose escalation part to model the dose-toxicity relationship of LDE225 and INC424 when given in combination. Dose recommendation will be based on summaries of the posterior distribution of model parameters and the posterior distribution of DLT rates. Following the principle of EWOC, after each cohort of patients the recommended dose combination is the one with the highest posterior probability of DLT in the target interval [16%, 35%) among the doses fulfilling the overdose-control criterion that there is less than 25% (posterior probability) chance of excessive toxicity. Phase II, the uniformly minimum variance unbiased estimator (UMVUE; Jung 2004) for the proportion of subjects achieving ≥ 35% reduction from baseline in spleen volume as measured by MRI/CT at 24 weeks and 48 weeks, and their exact two-sided 95% confidence intervals will be provided.
Key words	Myelofibrosis, Post-polycythemia vera myelofbrosis (Post PV-PMF), Post essential thrombocythemia myelofibrosis (Post ET-MF), Primary myelofibrosis (PMF), Intermediate risk myelofibrosis, High risk myelofibrosis, JAK inhibitor, smoothened inhibitor

[redacted]

1 Background

1.1 Overview of myelofibrosis and current treatment options

The four classic myeloproliferative neoplasms (MPNs) include chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF). Myelofibrosis (MF) can present as a de novo disorder (PMF) or evolve secondarily from previous PV or ET (post-PV MF or post-ET MF). Regardless of whether MF is a primary or secondary disorder, it is characterized by a clonal stem cell proliferation associated with production of elevated serum levels of multiple inflammatory and proangiogenic cytokines, a characteristic bone marrow stromal pattern that includes varying degrees of collagen fibrosis, osteosclerosis and angiogenesis and a peripheral blood smear showing a leukoerythroblastic pattern with varying degrees of circulating progenitor cells. Clinically, myelofibrosis is characterized by progressive anemia, leukopenia or leukocytosis, thrombocytopenia or thrombocythemia and multi-organ extramedullary hematopoiesis most prominently involving the liver and spleen. Patients may experience severe constitutional symptoms, sequelae of massive splenomegaly (pain, limitations of movement, early satiety and shortness of breath, hepatic obstruction, and splenic infarction), a hypermetabolic state with cachexia, progressive hematopoietic failure, progression to leukemia, and premature death.

MF is defined by the National Institutes of Health (NIH) as a "rare disease" with a prevalence of 0.3 to 1.5 cases per 100,000 with a median age at diagnosis of 65 years (Mesa 1999, Rollison 2008).

Survival in MF varies with the presence or absence of specific risk factors. A multi-center analysis of risk factors and their impact on prognosis in patients with MF have recently been published (Cervantes 2009). Age greater than 65 years, presence of constitutional symptoms (weight loss > 10% of the baseline value in the year preceding PMF diagnosis, unexplained fever, or excessive night sweats persisting for more than 1 month), anemia (Hemoglobin (Hgb) less than 10 g/dL), leukocytosis (white blood cell count (WBC) greater than 25 x10^9/L), and a circulating blast percentage of 1% or higher were identified as individually predictive of outcome. It was demonstrated that patients could be distinctly grouped into four categories without overlapping median survival curves based upon the number of risk factors (Table 1-1).

Recent studies have demonstrated that transfusion need in the first year of diagnosis or the presence of cytogenetic abnormalities other than sole +9, 13q-, or 20q- identifies patients with median survival of less than 5 years (Barbui 2011).

Table 1-1 Median survival of MF patients according to risk category

No of risk factors	Risk category	Median survival (months)
0	Low	135
1	Intermediate-1	95
2	Intermediate-2	48
3 or more	High	27

[redacted]

For a subset of patients who are younger (generally less than 65 years), otherwise healthy and have a histocompatible donor, allogeneic stem cell transplantation may provide a curative option. However, substantial risk of mortality has been reported in around 30% and 20% of patients for standard allogeneic and for reduced intensity allo-transplants, respectively (Ballen 2012). Drug therapies used, including hydroxyurea, busulfan, 6-mercaptopurine, anagrelide, thalidomide, lenalidomide, interferon, corticosteroids, and erythropoiesis stimulating agents or growth factors have not been shown to improve survival. Some can increase the risk of leukemic transformation, and/or are poorly tolerated, and all have limited effectiveness in improving splenomegaly and constitutional symptoms. One group determined that splenectomy, performed in approximately 10% of patients, is associated with significant morbidity and mortality (Cervantes 2009). Splenic irradiation is employed to reduce symptoms secondary to splenomegaly, but symptomatic improvement is variable and short-lived; moreover, transient and life-threatening pancytopenia and an approximate 20% treatment-related mortality have been noted.

Thrombocytopenia, although not found to be an independent variable in the multivariate analysis of prognostic factors proposed by the International Working Group for Myelofibrosis Research and Treatment (Cervantes 2009), is considered to be an adverse risk factor by the Mayo Clinic group (Elliott 2007). Apart from being an indicator of diminished bone marrow reserve, thrombocytopenia may also be a limiting factor with regards to therapy intensity with multiple agents, including INC424, which constitutes a Dose Limiting Toxicity (DLT). Therefore, thrombocytopenic patients are often excluded from investigational studies despite having MF requiring therapy. Hence, new treatments that can modify the disease and improve bone marrow reserve are needed.

1.2 Role of hedgehog signaling in cancer

Hedgehog (Hh) signaling plays a critical role in the development and homeostasis of many human organs and tissues (McMohan 2003).

In the resting state, the transmembrane protein Patched (PTCH) inhibits the activity of Smo. The Hh family protein ligands including sonic hedgehog (SHH), desert hedgehog (DHH) and Indian hedgehog (IHH) can all bind to and inactivate PTCH. Upon Hh ligand binding, activated Smo signals through a complex of cystolic proteins, resulting in the activation of Glioma-associated oncogene homolog (Gli) transcription factors and their subsequent nuclear translocation to induce Hh target genes, such as Gli 1, PTCH1, cyclin D1, bcl-2, N-myc, and secreted frizzled-related protein 1 (sFRP). The Gli transcription factors, the downstream effectors of Hh signaling (Teglund and Toftgard 2010), promote cell proliferation, differentiation, and survival (Pasca di Magliano and Hebrok 2003). Therefore, the expression of Gli1 messenger ribonucleic acid (mRNA) in tumor or relevant surrogate tissues constitute a reliable indicator of Hh pathway activity (Scales and Sauvage 2009).

Several lines of evidence support 3 mechanistic roles for Hh signaling in cancer: (1) a cancer cell-autonomous role, in which tumor growth is driven by activating mutations in the pathway; (2) paracrine signaling role involving tumor and stromal interactions that promote tumor growth and invasion; and (3) an autocrine signaling role via cancer stem cells that promotes self-renewal and proliferation (Shelton and Gilmartin 2009). Ultimately, the linkage of aberrant Hh signaling pathway to tumor genesis is thought to be mediated through cell-

[redacted]

cycle dysregulation, protection of cancer cells against apoptosis and modulation of angiogenesis (Scales and Sauvage 2009). Activating or inactivating mutations in genes that regulate the Hh pathway have been identified in approximately one-third of patients with medulloblastoma (MB) (mutations in PTCH, Smo and suppressor of fused (SuFu)), in >95% of patients with basal cell carcinoma (BCC) (mutations in PTCH or Smo), and in patients with rhabdomyosarcoma. In addition, aberrant upregulation of the Hh pathway via autocrine or paracrine signaling mechanisms is linked to a number of other tumor types, including pancreatic, small-cell lung cancer, (SCLC) and breast cancers as well as gliomas and CML.

It has been hypothesized that tumors are hierarchical structures, and that their capacity for initiation and propagation is limited to a small number of very primitive cells, the so called cancer stem cells (CSC). These cells are similar to their normal counterparts, and can proliferate and, in addition, give rise to a more differentiated progeny (Reya 2001). Such a population has been clearly demonstrated in CML and acute myeloid leukemia (AML), and there is also evidence of their existence in many other tumors, such as myeloma, lymphoma, glioblastoma, breast, and prostate cancer. CSCs are usually quiescent and therefore resistant to conventional therapies. Failure to effectively target these cells may result in residual low-level disease and the likelihood of future relapse (Irvine 2012).

Hh pathway activation has been shown in CD34+ cells from patients with chronic myeloproliferative disorders, as compared to healthy controls (measured through Gli1 and PTCH1 expression).

Thus, it is thought that combination treatment with inhibitors of JAK2 and Hh signaling may provide more clinical benefit than monotherapy with a JAK2 inhibitor, such as INC424.

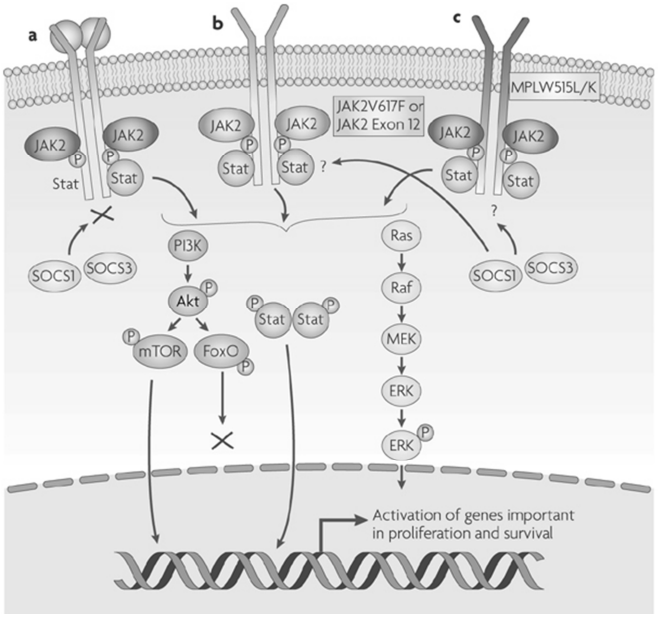
1.3 Janus kinases (JAKs) in myelofibrosis

A considerable number of cytokine and growth factor receptors utilize non-receptor tyrosine kinases, the Janus kinases (JAKs), to transmit extracellular ligand binding into an intracellular response (Figure 1-1) (Levine 2007). For example, erythropoietin, thrombopoietin and granulocyte monocyte colony stimulating factor are all known to signal through receptors that utilize *JAK2*. JAKs activate a number of downstream pathways implicated in proliferation and survival, including the STATs (signal transducers and activators of transcription), a family of important latent transcription factors.

Myelofibrosis is a clonal stem cell disease characterized by molecular (*JAK2*V617F, *MPL*W515L/K) and cytogenetic (13q-,20q-) markers (Pikman 2006, Scott 2007). The *JAK2*V617F mutation has been identified in over 95% of patients with PV and approximately 50% of patients with ET and PMF. Furthermore, in a preclinical setting, animal studies have demonstrated that this mutation can lead to an MF-like syndrome. The *JAK2*V617F mutation alters the *JAK2* tyrosine kinase making it constitutively active. As a result, polycythemia, thrombocythemia and leukocytosis can develop independently from growth factor regulation. Even in patients lacking a confirmed *JAK2* mutation, the detection of STAT activation suggests dysregulated *JAK* activity. In fact, regardless of the mutational status of *JAK2*, the

malignant cells appear to retain their responsiveness to *JAK* activating cytokines and/or growth factors; and therefore, may benefit from *JAK* inhibition.

Figure 1-1 Schematic representation of the JAK pathway



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

1.4.1 Overview of LDE225

LDE225 is a potent, selective and orally bioavailable inhibitor of Smo from a novel structural class N-[6-(cis-2,6-dimethylmorpholin-4-yl)pyridine-3-yl]-2-methyl-4'-(trifluoromethoxy)-1,1'-[biphenyl]-3-carboxamide diphosphate.

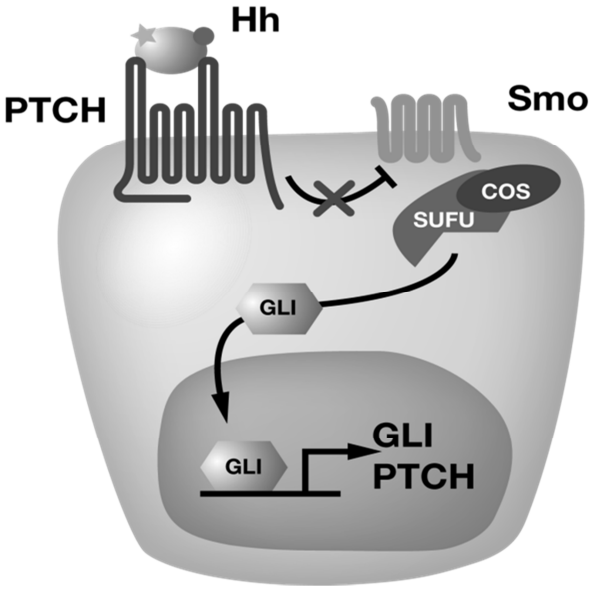
1.4.1.1 Non-clinical experience

1.4.1.1.1 Summary of basic pharmacology

LDE225 is a potent, selective and orally bioavailable Smo inhibitor, which is currently in early stages of clinical development. Smo is a GPCR-like membrane protein which activates the Hh signal transduction pathway (Figure 1-2). Physiologically, Smo is blocked by PTCH, the Hh-ligand specific cell surface receptor. Aberrant activation of Smo as a consequence of loss-of-function mutations of PTCH or gain-of-function mutations of Smo is associated with development of Hh-pathway dependent tumor types, including MB and BCC. The Hh-pathway is therefore an attractive target for therapeutic intervention.

[redacted]

Figure 1-2 Schematic representation of Smo activation of the Hh pathway



A number of *in vitro* studies have been conducted to characterize the pharmacological activity of LDE225. LDE225 is a high-affinity ligand for human and mouse Smo, as shown by its ability to displace radiolabeled Smo agonists, with an IC50 of 11 nM for human Smo and 12 nM for mouse Smo. In multiple cell-based assays, LDE225 is a potent antagonist of Hh-dependent pathway activation. It inhibits Hh-mediated Gli1 activation in mouse TM3 and human HEPM cells with an IC50 of 7 nM and 13 nM, respectively. LDE225 potently inhibits proliferation and Gli1 expression of freshly isolated mouse MB tumor cells *in vitro* with an IC50 of 7 nM.

Treatment with LDE225 results in tumor regression *in vivo* in several genetically defined MB models. Efficacy in these tumor models is dose-related and correlates with inhibition of Hh-pathway signaling, as measured by decreased Gli1 mRNA. LDE225 was well tolerated in mice with no significant body weight loss at all doses (up to 160 mg/kg daily (QD)) investigated. Treatment with LDE225 induced >87 % tumor regression at 20 mg/kg QD and 10 mg/kg twice daily (BID) in PTCH+/- p53-/-, PTCH+/- Hic+/- and PTCH+/- subcutaneous tumor allograft mouse MB models. Following cortical implantation of PTCH+/- p53-/- cells, tumor volume reduction and extension of time to progression was observed following treatment at a 20 mg/kg BID dose.

In vivo PK/PD analysis in PTCH+/- p53-/- and PTCH+/- Hic+/- MB models showed a good correlation between the given dose, the measured blood and tissue levels, the effects on the Hh-pathway as measured by Gli1 mRNA expression and the anti-tumor activity. It appeared that almost complete and sustained Gli1 mRNA inhibition (approximately 95%) was associated with tumor regression [LDE225 Investigator's Brochure (IB)].

1.4.1.1.2 Summary of non-clinical pharmacokinetics, metabolism and toxicity

LDE225 was well absorbed with good oral bioavailability, ranging from 68 to 100% in the mouse, rat, dog, and monkey after oral administration either in the form of a solution or a

[redacted]

diphosphate salt suspension. The clearance was low to moderate compared to the hepatic blood flow for all species studied. The compound was extensively distributed into tissues and its volume of distribution at steady state (Vss) was greater than total body water (1.9-7.0 L/kg). LDE225 exhibited high protein binding (approximately 98% in mouse, rat, dog and human plasma), independent of concentration. In rats, >85% of LDE225 related radioactivity was eliminated into the feces following both intravenous and oral administration, and renal excretion was minor, accounting for <3.0% of the administered dose.

LDE225 was extensively metabolized in rats, with the major metabolic pathway being via mono- or dioxygenation, demethylation, and oxidation leading to carboxylic acid formation, dealkylation, and dehydrogenation. Hepatic oxidative metabolism of LDE225 in vitro was mediated primarily by CYP3A4. The elimination of metabolites was mainly through the bile.

Studies with human liver microsomes showed inhibition of CYP2B6 (IC50 ~0.5 μM; K_i 0.045 μM) and CYP2C9 (IC50~5 μM; K_i 1.7 μM), but very little or no inhibition of CYP1A2, 2A6, 2C8, 2C19, 2D6, 2E1 or 3A4/5 at concentrations of up to 100 μM. No apparent time-dependent inhibition of the major CYP450 enzymes or induction of CYP3A4 was observed. LDE225 was neither a substrate nor an inhibitor of P-glycoprotein (P-gp) or multi-drug resistance protein 2 (MRP2); but it has demonstrated inhibitory effects on breast cancer resistance protein (BCRP), with an estimated IC50 value of 1.5 μM. The potential of LDE225 and its metabolites to undergo covalent binding to cellular macromolecules was found to be low.

The results of toxicokinetics (TK) studies with LDE225 indicated that systemic exposure after oral administration, as measured by Cmax and AUC generally increased less than dose-proportionally in both rats and dogs. There was drug accumulation after once daily repeat oral doses, which was more pronounced and dose-dependent in dogs. There was an apparent gender difference in exposure in rats following multiple dosing, with female rats exhibiting higher exposure than male rats.

The majority of adverse effects observed in the 4-wk Good Laboratory Practice (GLP) toxicity studies in growing rats and dogs can be attributed to the pharmacologic action of LDE225, and the effects in both species were similar. The most striking effects of LDE225 were on growing bone, and consisted of thinning or closure of growth plates in the sternum and femur. These effects are not likely to occur in the adult cancer patient population due to the maturity of their skeletal system. Likewise, effects on growing teeth in rats including dentine dysplasia of the incisors is not expected to occur in adult cancer patients. Other drug-related effects, likely associated with the pharmacology of LDE225, included effects on the male and female reproductive tract of young rats and dogs. Gastrointestinal (GI) toxicity was likely dose limiting in the animal studies. In the GLP juvenile rat study, minimal to slight degeneration of nerve fibers was found in the sciatic nerve and, less commonly, in the thoracic spinal cord, but not in the cervical or lumbar spinal cord or optic nerve. Effects on nerves were not seen in any of the toxicity studies on more mature rats or dogs. Consistent with the role of Hh signaling in embryo-fetal development, LDE225 was shown to be teratogenic, an expected class effect of Smo inhibitors. LDE225 was not genotoxic in studies conducted *in vitro* and *in vivo*, and showed no potential risk for phototoxicity.

[redacted]

For more details on the non-clinical toxicity, toxicokinetics and safety of LDE225 refer to the [LDE225 Investigator's Brochure].

1.4.1.2 Clinical experience

1.4.1.2.1 Clinical safety and efficacy

The safety and preliminary efficacy of single-agent oral LDE225 in cancer patients has been assessed in three early phase studies ([CLDE225X2101], [CLDE225X2104] and [CLDE225X1101]). A summary of the safety, PK and PD data from study [CLDE225X2101] is provided in this section, as it has completed accrual and has the most mature data set.

LDE225 has been evaluated in a first-in-human, phase I, multicenter open-label dose escalation study [CLDE225X2101] in patients with advanced solid tumors including medulloblastoma that have progressed despite standard treatments or have no existing therapies. The primary objective was to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and potential efficacy of continuous once daily oral administration. This study has completed enrollment.

As of November 29, 2014, a total of 1381 patients, including patients with various cancers and 62 pediatric patients, received LDE225 at various dose levels, administered daily up to 3000 mg/day.

Oral LDE225 is generally well tolerated. The maximum tolerated dose (MTD) was determined to be 800 mg QD and 250 mg BID. The twice daily dosing regimen did not appear to offer any advantage over once daily, hence the recommended dose of LDE225 in adults is 800 mg QD. Across all dose levels, grade 3 or 4 adverse events (AEs) suspected to be treatment-related were uncommon, except dose-limiting muscle toxicity (Table 1-2). Commonly reported Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 adverse events suspected to be treatment-related include: nausea, vomiting, dysgeusia, decreased appetite, myalgia, muscle spasms and fatigue (Table 1-3).

DLTs that are characterized by CTCAE grade 3 or 4 increases in plasma creatine phosphokinase (CK) were observed at once daily doses ≥ 800 mg and twice daily doses ≥ 250 mg in an exposure-dependent manner (Table 1-2 and Figure 1-3). The higher incidence of the DLTs in the BID cohorts when compared with QD cohorts of the same total daily dose is consistent with the comparatively higher systemic drug exposures obtained with the BID schedule (Section 1.4.1.2.3). Some of the patients who experienced muscle toxicity also had grade 3 or 4 elevated serum AST and ALT. The majority of the DLT events occurred during the initial 4-6 weeks of treatment with LDE225, except for three events that were observed after 6 weeks. None of the patients experienced impairment of renal function as a result of this toxicity. The DLTs resolved within 4-8 weeks following discontinuation of LDE225 therapy. Of the 19 patients with Grade 3/4 CK elevations, 8 patients resumed treatment at reduced doses and none had subsequent Grade 3/4 CK elevations.

[redacted]

Table 1-2 Incidence of dose limiting toxicities in study CLDE225X2101

Dose of LDE225	Number of patients treated	Elevated plasma CK		
		Number of patients with CTCAE grade 3	Number of patients with CTCAE grade 4	Total (CTCAE grade 3 or 4)
100 mg QD	6	0	0	0
200 mg QD	6	0	0	0
400 mg QD	5	0	0	0
800 mg QD	26	1	1	2
1000 mg QD	11	1	1	2
1500 mg QD	9	0	3	3
3000 mg QD	10	0	3	3
250 mg BID	14	1	1	2
400 mg BID	8	1	1	2
750 mg BID	8	0	5	5
Total	103	4	15	19

No treatment-related clinically significant changes in the other safety laboratory data (hematology, and urinalysis), vital signs or electrocardiograms (ECGs) have been observed for any of the patients treated in the study. Refer to [LDE225 Investigator's Brochure] for further details.

Table 1-3 Adverse events suspected to be related to LDE225 by preferred term, occurring in 5% or more of patients in study CLDE225X2101

	800 mg QD* (n=26)		All doses** (n=103)	
	All Grades	Grade 3/4	All Grades	Grade ¾
Blood CK increased	7 (26.9)	2 (7.7)	33 (32.0)	19 (18.4)
Muscle spasms	9 (34.6)	0 (0.0)	33 (32.0)	0 (0.0)
Dysgeusia	5 (19.2)	0 (0.0)	30 (29.1)	0 (0.0)
Nausea	4 (15.4)	0 (0.0)	26 (25.2)	0 (0.0)
Decreased appetite	4 (15.4)	0 (0.0)	19 (18.4)	0 (0.0)
Myalgia	4 (15.4)	0 (0.0)	17 (16.5)	1 (1.0)
Fatigue	1 (3.8)	0 (0.0)	15 (14.6)	0 (0.0)
Alopecia	4 (15.4)	0 (0.0)	13 (12.6)	0 (0.0)
Asthenia	5 (19.2)	1 (3.8)	13 (12.6)	3 (2.9)
Vomiting	3 (11.5)	0 (0.0)	13 (12.6)	0 (0.0)
Weight decreased	4 (15.4)	1 (3.8)	11 (10.7)	1 (1.0)
AST increased	1 (3.8)	0 (0.0)	8 (7.8)	4 (3.9)
ALT increased	1 (3.8)	0 (0.0)	7 (6.8)	3 (2.9)
Diarrhea	2 (7.7)	0 (0.0)	7 (6.8)	0 (0.0)
Lethargy	3 (11.5)	0 (0.0)	7 (6.8)	0 (0.0)
Constipation	1 (3.8)	0 (0.0)	6 (5.8)	0 (0.0)

*Maximum tolerated dose in adults
**All doses, including BID and QD schedule

[redacted]

1.4.1.2.2 Clinical efficacy from Study CLDE225X2101

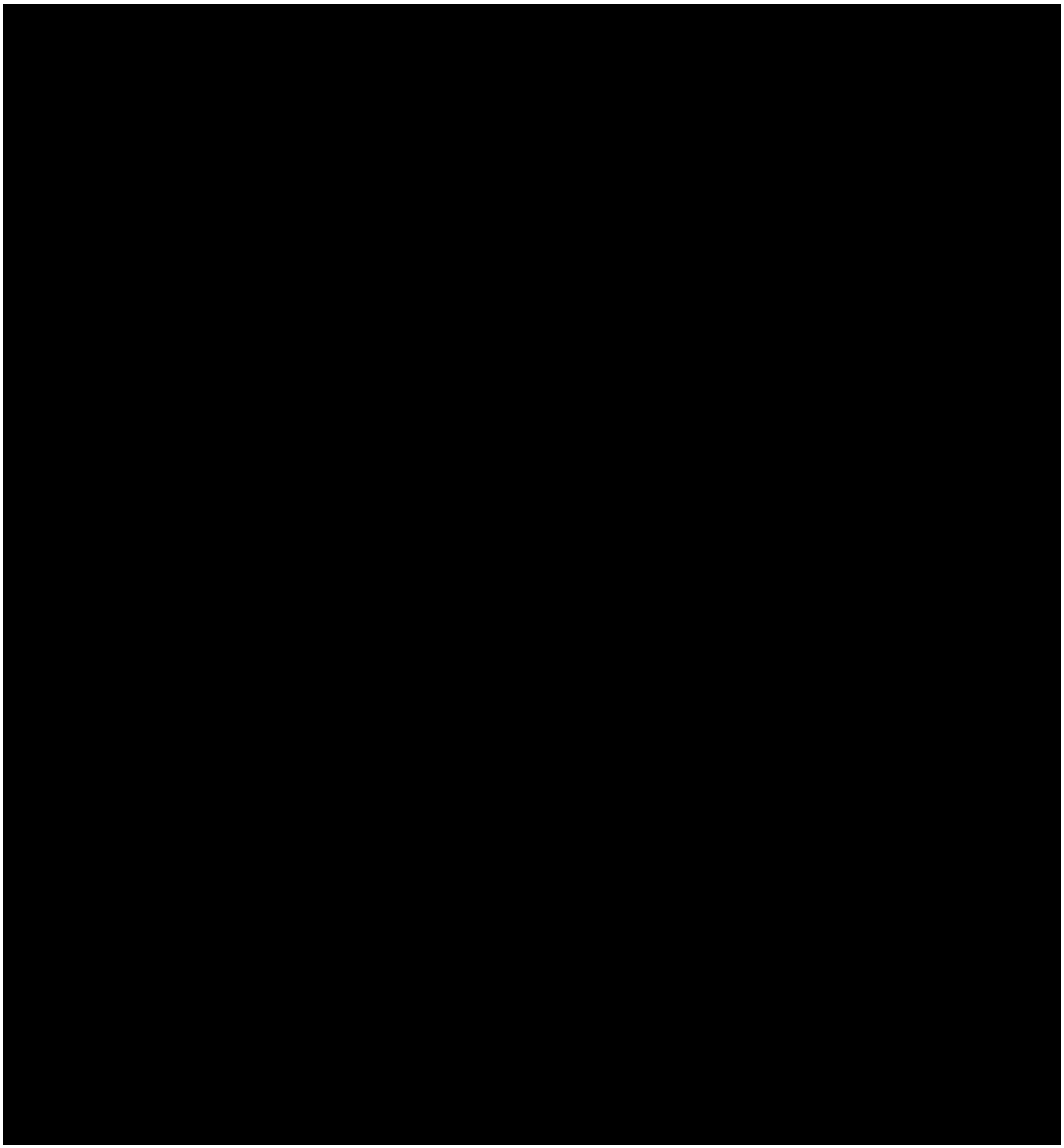
Preliminary antitumor activity and evidence of disease stabilization has been observed with LDE225 treatment. As of March 2012, 9 adult patients with recurrent MB have been treated in the ongoing phase I studies of LDE225 in advanced solid tumors (studies [CLDE225X2101] [EU/US] and [CLDE225X1101] [Asia]). Of these, 3 patients achieved confirmed partial tumor responses at 200 mg QD (by Response Evaluation Criteria In Solid Tumors, RECIST), 800 mg QD (by RECIST) and 1500 mg QD (by FDG-PET) and remained on treatment for approximately 6, 9 and 10 months respectively. All the MB patients are off therapy due to disease progression (Table 1-4).

Table 1-4 Anti-tumor activity in adult patients with recurrent medulloblastoma

Patient	Dose	Overall Best Response	Time on Study
[redacted]	100 mg QD	PD	1 month
	200 mg QD	PR	6 months
	200 mg QD	PD	2 months
	800 mg QD	SD	4 months
	800 mg QD	PR	9 months
	800 mg QD	PD	2.5 months
	1500 mg QD	PD	2 months
	1500 mg QD	PMR	10 months
	250 mg BID	PD	2 months

PD, disease progression; PMR partial metabolic response; PR, partial response; SD, stable disease.

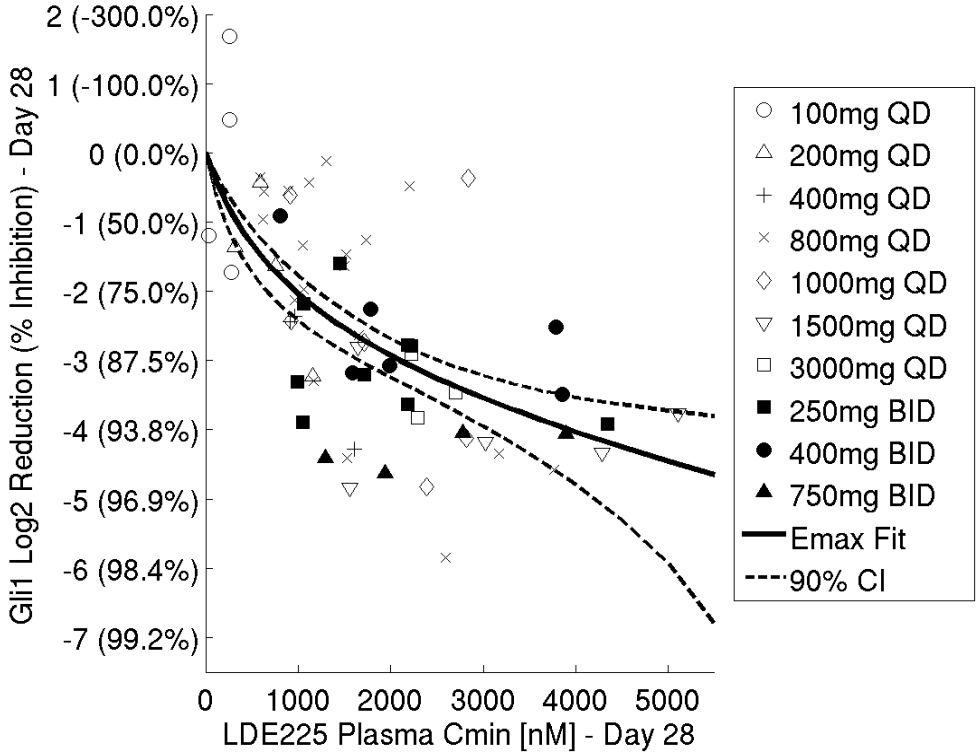
[redacted]



1.4.1.2.4 Effect of LDE225 treatment on Gli1 mRNA expression

In study [CLDE225X2101], analyses of skin punch biopsies taken at baseline and at the end of the first treatment cycle have shown evidence of potent target modulation, as measured by Gli1 mRNA, in a dose- and exposure (Cmin) dependent manner (Figure 1-4). The available data shows that LDE225 caused up to 98% mean reduction in Gli1 expression in skin compared with baseline values. An Emax model [Inhibition = Emax*Cmin/(EC50+Cmin)] was fit to the Cmin and Gli-1 log reduction data at Day 28. We found a significant dependency of Gli-1 inhibition on Cmin at Day 28, with a maximum inhibition (Emax) between 90%–100%.

Figure 1-4 Pk-Gli1 inhibition relationship to LDE225



1.4.2 Overview of INC424 (ruxolitinib)

INC424 phosphate, designated INC424 throughout, is a novel, potent, reversible and selective inhibitor of JAK1- and JAK2-STAT signaling (Quintas-Cardama 2010) that is currently under development for treatment of MPNs and advanced hematologic malignancies. INC424 is approved in more than 70 countries including the USA, Canada and the EU with the following indication wording:

USA (under the trade name of Jakafi): INC424 is intended for the treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF) and post-essential thrombocythemia myelofibrosis (post-ET MF). INC424 is also indicated for treatment of patients with Polycythemia Vera who have had an inadequate response to or are intolerant of hydroxyurea.

Canada (under the trade name of Jakavi): Jakavi is indicated for the treatment of splenomegaly and/or its associated symptoms in adult patients with PMF (also known as Chronic idiopathic myelofibrosis (CIM), post-PV MF or post-ET MF.

EU (under the trade name of Jakavi): Jakavi is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with PMF (also known as CIM), post-PV MF or post-ET MF.

1.4.2.1 Non-clinical experience

INC424 inhibited the splenomegaly and morbidity/mortality in mice resulting from intravenous inoculation of cells expressing the same mutated JAK2 (V617F) implicated in the pathogenesis of the majority of Philadelphia chromosome negative MPNs (Quintas-Cardama 2010).

[redacted]

Based on safety pharmacology studies and on the results of clinical studies, the potential for INC424 to cause adverse alterations in respiratory, neurologic, and cardiovascular parameters in humans is low.

In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated. INC424 was not teratogenic in either rat or rabbit. No effects were noted on reproductive performance or fertility in male or female rats. Increases in post-implantation loss were noted at the higher doses. In a pre- and post-natal development and maternal function study in rats there were no adverse findings for fertility indices or for maternal and embryo-fetal survival, growth, and developmental parameters. INC424 passed into the milk of lactating rats with an exposure that was 13-fold higher than maternal plasma exposure

INC424 was not mutagenic or clastogenic nor did it demonstrate potential for carcinogenicity in a 6-month study in Tg.rasH2 mice or in the 2-year rat study.

More detailed information on pharmacology of INC424, single and multiple dose PK studies conducted in multiple species and nonclinical safety evaluations can be found in the INC424 IB.

1.4.2.2 Clinical experience

As of July 2014, approximately 6,734 patients and healthy volunteers have been exposed to INC424. Please refer to the latest IB for details.

1.4.2.2.1 Human safety and tolerability data

In single dose studies, INC424 has a well-established safety profile and has been well tolerated with adverse events generally mild in intensity, reversible and of similar incidence following INC424 treatment compared with placebo or with other control treatments.

A definitive QT study was carried out in 50 healthy volunteers, evaluating the effects of single doses of 25 mg or 200 mg INC424 compared with placebo and 400 mg moxifloxacin (positive control). The overall conclusion was that there appeared to be no adverse impact on ECG signaling (little change in heart rate, QRS duration, QTcF interval, and a slight, non-clinically significant, increase in PR interval) with the administration of INC424.

In a 10-day multiple dose study, [INCB 18424-132] a total of 71 healthy volunteers in 6 cohorts received doses of 50 mg QD, 100 mg QD, 15 mg BID, 25 mg BID or 50 mg BID. INC424 or placebo. INC424 was well tolerated in the study, with most AEs reported equally

[redacted]

by both INC424-treated and placebo-treated volunteers. Neutropenia was noted in 3 volunteers receiving the highest dose of INC424, 50 mg BID. Neutropenia at the Grade 4 level led to study drug discontinuation on Day 5 in one volunteer and was reported as a Serious Adverse Event (SAE). There was a decline in mean absolute neutrophil count (ANC) and, to a lesser extent, in mean WBC count values with INC424 doses of 15 mg BID or higher. In general ANC or WBC returned to Baseline levels within 1 to 2 days following the last dose of study drug. Doses of 25 mg BID and 100 mg QD were determined to be the MTDs in this study based on the DLT of neutropenia.

Based on three studies [INCB 18424-351], [INCB 18424-251], [CINC424A2352], in the myelofibrosis population the majority of adverse events regardless of study drug relationship were grade 1 or 2 thrombocytopenia and anemia. The overall frequency of adverse events leading to study drug discontinuation was 10%, with 1.4% from thrombocytopenia, 1.2% from anemia, 0.8% from acute myeloid leukemia, and 0.6% from pneumonia. The overall frequency of adverse events requiring dose reduction or interruption was 55.4%, with 32.4% from thrombocytopenia, 10.4% from anemia, and 4.9% from platelet count decrease.

Details on anemia, thrombocytopenia, neutropenia, urinary tract infections, herpes zoster, tuberculosis, and increased systolic blood pressure as side effects of INC424 are presented below.

Anemia

In two pivotal myelofibrosis clinical studies, [INCB 18424-351] and [CINC424A2352], anemia of any CTCAE grade was observed in 82.4% of patients. The median time to onset of the first CTCAE grade 2 or higher anemia was 1.5 months in Phase III studies, with one patient (0.3%) discontinuing treatment due to anemia. In the randomized, placebo-controlled study [INCB 18424-351], 59.4% of INC424-treated patients and 37.1% of patients receiving placebo received red blood cell transfusions during randomized treatment. In the [CINC424A2352] study, the rate of packed red blood cell transfusions was 54.1% in the INC424 arm and 38.4% in the best-available therapy arm.

In patients receiving INC424, mean decreases of Hgb reached a nadir of approximately 15 to 20g/L below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 10 g/L below baseline.

Thrombocytopenia

In two pivotal myelofibrosis clinical studies, [INCB 18424-351] and [CINC424A2352], thrombocytopenia of any CTCAE grade was observed in 69.8% of patients. The median time to onset for patients who experienced grade 3 or 4 thrombocytopenia was 8 weeks, which was generally reversible with dose reduction or dose interruption. The median time to platelet recovery above 50 x 10^9/L was 14 days. Platelet transfusions were administered to 4.5% of patients receiving INC424 and 5.8% of patients receiving control regimens. Patients with a platelet count of 100 x 10^9/L to 200 x 10^9/L before starting INC424 treatment had a higher frequency of grade 3 or 4 thrombocytopenia compared to patients with platelet counts over 200 x 10^9/L, of 64.2% versus 35.4%.

[redacted]

Neutropenia

In two pivotal myelofibrosis clinical studies, [INCB 18424-351] and [CINC424A2352], neutropenia of any CTCAE grade was observed in 16.6% of patients. The median time of onset for patients experiencing grade 3 or 4 neutropenia was 12 weeks. In Phase III myelofibrosis studies, the dose was held or reduced in 1.3% of patients due to neutropenia. Treatment was discontinued in 0.3% of patients due to neutropenia.

Urinary tract infection

In Phase III myelofibrosis clinical studies, grade 3 or 4 urinary tract infection was reported for 1.0% of patients. Additionally, urosepsis was reported in 1.0% of patients and kidney infection was reported in one patient.

Herpes zoster

In Phase III myelofibrosis clinical studies, grade 3 or 4 herpes zoster infection was reported in one patient.

Tuberculosis

In Phase III myelofibrosis studies, tuberculosis of any grade was reported in 1.0 % of patients. Potential confounding factors include exposure to corticosteroids and history of hematological malignancies, diabetes, emphysema, BMI below 20 kg/m^2, asthma, bronchitis, and smoking as risk factors in the general population. Relation to INC424 is not clear due to the low number of cases and potential confounding factors involved.

Increased systolic blood pressure

In the phase III pivotal clinical studies an increase in systolic blood pressure of 20 mmHg or more from baseline was recorded in 31.5% of patients on at least one visit compared with 19.5% of the control-treated patients. Relation to INC424 is not clear at this point.

PML (progressive multifocal leukoencephalopathy)

One case of PML has been reported in a myelofibrosis patient receiving INC424. It would be important to note that an atypical feature of this disease occurred quickly (approximately one month) after initiation of INC424 treatment. Infections are well known complications in myelofibrosis patients. PML has been reported in myeloproliferative disease patients who are not taking INC424.

1.4.2.2.2 Human pharmacokinetic and metabolism data

INC424 exhibits near-complete absorption with maximal plasma concentration (Cmax) achieved approximately 1 hour after a single oral dose. Linearity in PK was demonstrated over a dose range of 5 to 200 mg following single-dose administration. PK parameters were similar between single and multiple doses. A drug accumulation ratio of 1.12 was observed following twice daily dosing. The effect of food on the INC424 exposure (4% increase in AUC, 90% confidence interval, CI 96.8 – 113%) is not expected to be clinically significant.

[redacted]

INC424 may be administered without regard to meals. INC424 is eliminated almost completely by oxidative metabolism with a terminal elimination half-life of approximately 3 h. INC424 is excreted in urine and feces with less than 1% excreted as unchanged parent drug.

In vitro metabolism studies showed that CYP3A4 was the predominant human CYP isozyme responsible for the metabolism of INC424 with minor contribution from CYP2C9. Systemic co-administration of oral ketoconazole, a potent CYP3A4 inhibitor, resulted in a 91% increase of plasma AUC, whereas erythromycin, a moderate CYP3A4 inhibitor, caused a 27% increase in exposure. Based on these results, the dose of INC424 should be decreased by approximately 50% when a potent CYP3A4 inhibitor is concomitantly used and no dose adjustment is necessary when a mild or moderate CYP3A4 inhibitor is used. INC424 is not known to induce or inhibit other CYP enzymes.

1.4.2.2.3 Clinical efficacy data

Results from two Phase III studies [INCB 18424-351] and [CINC424A2352] demonstrate the effectiveness of INC424 in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis. Both studies met their primary endpoint of ≥ 35% spleen volume reduction compared with either placebo or best available therapy (BAT). Starting doses for both studies were 15 mg BID for patients with baseline platelet counts of 100 to 200 x 10^9/L, and 20 mg BID for patients with baseline platelet counts of > 200 x 10^9/L. The splenic reduction timepoint for both studies occurred at different timepoints: Week 24 in [INCB 18424-351] and Week 48 in [CINC424A2352]. However, the mean volumetric spleen reduction are similar at Week 24, with 31.6% in [INCB 18424-251]and 29.2% in [CINC424A2352].

The volumetric spleen reduction also showed a favorable duration of response. Of the 80 patients from [INCB 18424-351] and the 69 patients from [CINC424A2352] that showed a ≥ 35% spleen volume reduction at any timepoint, the probability of maintaining a response on INC424 for at least 24 weeks was 89% for [INCB 18424-351] and 87% for [CINC424A2352], and the probability for maintaining a response for at least 48 weeks was 52% in [CINC424A2352].

Table 1-6 Volumetric spleen reduction of >/= 35% from baseline to Week 24 (INCB 18424-351) and Week 48 (CINC424A2352)

INCB 18424-351	**INC424 (N=155)**	**Placebo (N=154)**
Patients with ≥35% spleen volume reduction at Week 24	65 (41.9%)	1 (0.7%)
CINC424A2352	INC424 (N=144)	BAT (n=72)
Patients with ≥35% spleen volume reduction at Week 48	41 (28.5%)	0

The results of the two pivotal studies can be summarized as follows. Both pivotal registration studies [INCB 18424-351] and [CINC424A2352] (COMFORT-I and COMFORT-II) met their primary and secondary endpoints, with the expected exception of the secondary endpoint of OS in Study [INCB 18424-351]:

- In both studies, a statistically significantly larger proportion of patients randomized to INC424 achieved a ≥ 35% reduction from baseline in spleen volume compared to patients randomized to control. This effect was seen at both Week 24, 41.9% vs. 0.7% for placebo

[redacted]

(primary endpoint in COMFORT-I) and Week 48, 28.5% vs. 0% for BAT (primary endpoint in COMFORT-II).

- The key secondary endpoint in COMFORT-II was met; 31.9% of patients in the INC424 arm vs. 0% of patients in the BAT arm achieved a ≥ 35% reduction from baseline in spleen volume at Week 24.
- In both studies, a similar median and mean reduction in spleen volume at Week 24 was achieved of 33% (median) and 31.6% (mean) on COMFORT-I and of 28.4% (median) and 30.1% (mean) on COMFORT-II.
- In both studies, nearly all patients treated with INC424 had some decrease in spleen size over time, in contrast to the patients treated with placebo or BAT, who had mean increases in spleen volume: 8.1% at Week 24 on placebo, and 7.3% at Week 48 on BAT.
- In both studies, the reduction in spleen volume was durable. The probability of maintaining a response after onset of spleen volume response was 89% in COMFORT-II for 24 weeks and 52% in COMFORT-II for 48 weeks.
- In COMFORT-I, where symptom scores were measured in a double-blind, placebo controlled fashion, a significantly larger proportion of patients in the INC424 arm achieved a ≥ 50% improvement from baseline in Week 24 total MF symptom score compared to the placebo arm (45.9% vs. 5.3%, $p<0.0001$). In addition, the INC424 arm showed a significantly larger ($p<0.0001$) mean improvement from baseline in the Week 24 total symptom score (46.1% improvement). In contrast, the mean total symptom score in the placebo arm worsened over time (41.8% worsening).
    1. The improvement in MF symptoms was rapid. The median time to 50% reduction in total symptom score among patients achieving this level was 4.4 weeks.
    2. The INC424 arm had significantly greater mean percent improvement from baseline in the individual symptoms studied: night sweats, itching, abdominal discomfort, pain under ribs on left, feeling of fullness (early satiety), muscle/bone pain, and degree of inactivity. In contrast, the placebo arm showed worsening in all 6 individual symptoms as well as inactivity.
- In both studies, the INC424 arm showed clinically significant improvement in quality of life as measured by the European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire C30 (EORTC QLQ-C30).
- Neither study was powered to demonstrate a statistically significant difference in Overall Survival (OS) between the two arms. Though based on a low total number of events, in both studies the hazard ratio (95% confidence interval) for OS was directionally in favor of INC424 (COMFORT-I: HR=0.67 (95% CI: 0.30, 1.50); COMFORT-II: HR=0.7 (95% CI: 0.20, 2.49), although confidence intervals all cross one. Kaplan–Meier estimates, including 4 months of additional follow-up after the primary analysis for COMFORT-I, show a survival advantage for INC424 (HR= 0.50; 95% CI: 0.25 to 0.98; P=0.04).
- In subgroup analyses of the primary endpoint, INC424 was more effective than control (placebo in COMFORT-I and BAT in COMFORT-II) regardless of the presence or absence of the JAK2V617F mutation.

Regardless of the control treatment used (placebo or BAT); a significantly larger proportion of patients in the INC424 arm achieved a ≥ 35% reduction from baseline in spleen volume

[redacted]

compared with the control arm. This was observed at both Week 24 (primary endpoint in COMFORT-I) and Week 48 (primary endpoint in COMFORT-II).

Nearly all patients treated with INC424 in both studies had some decrease in spleen size over time, whereas the majority of patients treated with placebo in COMFORT-I and majority of patients treated with BAT in COMFORT-II had an increase in spleen size over time. Patients treated on the control arm of COMFORT-II received the most active therapy available to them and these treatments represent a typical pattern of therapies, including a preponderance of patients receiving hydroxyurea and smaller numbers treated with other treatments; cytotoxics, erythropoietic-stimulating agents, glucocorticoids, interferons, and purine analogues. Despite these therapies, 44% of patients had an increase in their spleen volume as their best response to therapy. Among all patients treated with BAT, including the 56% who had some reduction in spleen volume as their best response to therapy, there is still a net 8.5% median increase in spleen volume at Week 48.

In COMFORT-I, symptom scores were measured with an instrument specifically developed and validated for patients with MF and MPNs (Scherber 2011), the Modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 diary. In this double-blind, placebo-controlled study, a significantly larger proportion of patients in the INC424 arm achieved a $\geq$ 50% improvement from baseline in the Week 24 total symptom score compared with the placebo arm. In addition, the INC424 arm had a significantly larger mean and median improvement from baseline in Week 24 total symptom score compared with the placebo arm. The placebo arm showed mean and median worsening over time. The improvement in MF symptoms was rapid; the median time to 50% reduction in total symptom score was less than 4 weeks among patients achieving this level of improvement. The INC424 arm had significantly greater mean percent improvement from baseline in the individual symptoms queried as part of the modified MFSAF v2.0 diary (night sweats, itching, abdominal discomfort, pain under ribs on left, feeling of fullness (early satiety), muscle/bone pain, and degree of inactivity [degree of inactivity was not part of the total symptom score]) compared with the placebo arm, which had a worsening, for all 6 of the individual symptoms as well as inactivity. The INC424 arm showed significant improvement in quality of life as measured by the EORTC QLQ-C30 in COMFORT-I, which was supported by similar patient reported outcome results in COMFORT-II.

The aforementioned improvements in quality of life have been measured in a variety of ways with validated patient-reported outcome instruments and demonstrate consistent findings of the beneficial effect of INC424 for patients with MF with regard to improvement or resolution of constitutional symptoms, relief of abdominal pain and discomfort, improvement in appetite and restoration of more normal weight, and generally improved functional activity. Apart from the beneficial effects of INC424 on decreasing splenomegaly and, therefore, extramedullary hematopoiesis, these additional beneficial effects on patients' quality of life are clinically relevant.

Longer-term outcomes such as Leukemia-Free Survival (LFS) and OS were not expected to show benefits over this period of follow-up. No detriment in long-term outcomes was seen, and follow-up will continue despite being affected by the cross-over design of both studies.

[redacted]

The consistency of efficacy findings, especially with regard to mean and median spleen volume reductions at the respective primary endpoints of 24 and 48 weeks is reassuring for estimating the potential benefits of INC424 and its durability of response. Importantly, other endpoints including symptom assessments, spleen length, and body weight all demonstrate a clinically important and beneficial effect of treatment with INC424. These improvements are all manifested early in the course of treatment and are durable over 24 and 48 weeks in the respective Phase III studies. This translates into an overall benefit for patients with MF, both in the rapid and durable reduction of extramedullary hematopoiesis that is the direct consequence of bone marrow fibrosis and in the marked improvement or resolution of constitutional and other symptoms that helps to restore a more normal quality of life.

The results from these two adequate and well-controlled Phase III studies demonstrated the efficacy of INC424 in patients with PMF, post-PV MF or post-ET MF.

Additional details for INC424 may be found in the [INC424 Investigator's Brochure].

2 Rationale

2.1 Study rationale and purpose

Myelofibrosis is a clonal proliferative disease of hematopoietic stem cells driven by a dysregulated and overactive Janus Activating Kinase 2 (JAK) pathway, leading to an inappropriate cytokine release, fibrosis of the bone marrow, constitutive mobilization of committed progenitor cells into the peripheral blood, and extra-medullary hematopoiesis, mainly expressed as prominent splenomegaly (Rambaldi 2008).

INC424 is a preferential JAK1 and JAK2 inhibitor with selectivity over other kinases. Data from a Phase I/II study in MF (INCB 18424-251) showed that 57% of patients treated obtained at least a 50% reduction in palpable spleen protrusion below the left costal margin corresponding to an approximate 35% reduction in volumetric spleen size, and tolerated doses up to 25 mg BID, with activity seen at multiple dose levels from 5 mg BID to 25 mg BID. Data from this phase I/II study showed patient responses independent of the JAK2 mutation, which is consistent with dysregulated JAK signaling in MF patients. Within 1 month of initiating treatment, levels of pro-inflammatory cytokines and angiogenic growth factors were reduced, and patients noted improvement in symptoms. This improvement in symptoms was even seen at the lowest end of the dosing spectrum (10 mg BID) when clinically noticeable reduction in splenic size was rarely seen. Results from the phase I/II study were confirmed by two randomized phase III trials (COMFORT-I and COMFORT-II) that met their primary and secondary end points with high statistical significance (See Section 1.4.2.2.3).

It has been observed that Hh target genes (Gli1 and PTCH1) are overexpressed in primary MPN cells from patients. While JAK2 inhibition of a preclinical model of MF (MPLW515L) has been shown to attenuate Hh signaling, the latter is not completely shut down. [redacted]

Furthermore, encouraging clinical activity, in terms of post-treatment reduction in reticulin staining in a bone marrow sample, has been reported in a phase I dose escalation study of an [redacted]

oral Hh inhibitor as single agent, in 1 out of 6 patients with myelofibrosis (Jamieson 2011). This data suggest that Hh inhibition may have the potential to modify the disease process through reduction in bone marrow fibrosis.

Taken together, it is thought that the combination of LDE225 and INC424 could potentially provide improved clinical benefit to patients. Therefore, the purpose of this study is to determine the MTD/RPIID and to assess the safety and efficacy of the LDE225 and INC424 combination in MF patients.

2.2 Rationale for the study design

A Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle will be employed in the Phase Ib part of the study to determine the MTD and/or RPIID of the oral co-administration of LDE225 and INC424. This is an established method for dose escalation in oncology trials and is used extensively as a means of avoiding excessive toxicity. The dose escalation process will determine the safety and tolerability of the oral co-administration, as well as assess PK/PD interactions and preliminary efficacy based on palpable splenic length reduction at each dose level. The initial doses selected are lower than the respective MTD and/or clinically approved doses. Once the combined doses are found to be well tolerated, dose increment will be implemented one agent at a time to minimize potential difficulties in determining the attribution of causality of treatment-emergent adverse events.

Although the COMFORT I and II trials only enrolled patients with platelet counts $\geq$ 100x10^9/L, patients with baseline platelet counts $\geq$ 75 x10^9/L will be allowed to enroll in this combination study. This is supported by the fact at least 20% of the exposure in the COMFORT II trial has been in patients experiencing thrombocytopenia. Furthermore, there is emerging evidence, from an ongoing Phase I trial, suggesting that patients with platelets $\geq$ 50 x 10^9/L can tolerate increasing doses of ruxolitinib (INC424) without thrombocytopenia-related DLTs (Expand: a Phase 1b, Open-Label, Dose-Finding Study of Ruxolitinib in Patients with Myelofibrosis and Baseline Platelet Counts Between 50 $\times$ 10^9/L and 99 $\times$ 10^9/L study [CINC424A2201-NCT01317875]).

Finally, it is hypothesized that LDE225 could reduce bone marrow fibrosis and lead to reductions in the doses of INC424 necessary to achieve therapeutic benefit, with the corresponding decrease in drug-induced cytopenias.

Once the MTD and/or RPIID is determined a safety expansion cohort of 6 patients will be enrolled at that dose level to further define the safety and tolerability of the combination. If two MTDs/RPIIDs are established, then patients enrolled in the Phase II portion will receive the corresponding dose based on their baseline platelet counts.

The efficacy of the co-administration of LDE225 and INC424, as determined by splenic volume reduction from baseline, will be evaluated using a Bayesian predictive probability of success (PPOS) index during the phase II portion of the study. Phase II will have a two-stage design. In phase II, encouraging efficacy will be concluded if the proportion of patients achieving a $\geq$ 35% reduction in spleen volume from baseline, as measured by MRI/CT at 24 weeks, is $\geq$ 50%. At the initial stage (stage 1), 18 patients will be enrolled. An interim analysis will be conducted after the 18 patients in Stage 1 have been observed for 24 weeks or

until death, documented disease progression, initiation of a new MF therapy, intolerable toxicity, withdrawal of consent, discontinuation at the discretion of the investigator or lost to follow-up. If the PPOS exceeds 20% based on Stage 1 patients, equivalent to observing at least 8 responders (i.e., spleen volumetric reduction of at least 35% through MRI/CT) observed over a 24 week period, an additional 28 patients will be enrolled into Stage 2. Encouraging efficacy will be concluded if the observed Overall Response Rate (ORR) exceeds 50% (i.e. 23/46). Additionally, in this Phase II part, the effect of the combination of bone marrow fibrosis and disease-specific pharmacodynamics biomarkers as a function of the molecular disease characterization of myelofibrosis will be evaluated to support the development of patient pre-selection markers.

2.3 Rationale for dose and regimen selection

The MTD of LDE225 (800 mg QD) and approved INC424 doses (15 mg or 20 mg BID) as single agents have been previously established in several phase I and later stage studies, respectively.

Since this is the first co-administration study with LDE225 and INC424, starting doses that are lower than the respective MTD and/or clinically approved doses have been chosen (LDE225 400 mg QD plus INC424 10 mg BID). Preliminary clinical safety data from the single-agent studies of LDE225 and INC424 do not suggest a tendency for significant overlapping toxicities. In particular, no evidence of bone marrow suppression has been observed with LDE225 monotherapy, up to 3000 mg QD. Thus, the starting dose and regimen are considered safe.

Both LDE225 and INC424 are primarily metabolized by CYP3A4. In vitro, LDE225 did not inhibit CYP1A2, 2A6, 2C8, 2C19, 2D6, 2E1 or 3A4/5 at concentrations of up to 100 μM, which is much higher than the expected steady-state Cmax of approximately 3 μM based on the preliminary population PK model at 800mg QD. No apparent time-dependent inhibition of the major CYP450 enzymes or induction of CYP3A4 was observed. LDE225 was found to be an inhibitor of CYP2B6 which did not contribute to INC424 turnover. LDE225 was also found to be an inhibitor of CYP2C9. Since CYP2C9 is a minor metabolic pathway of INC424, the inhibition effect from LDE225 is not expected to be clinically significant. Therefore, LDE225 is not expected to affect the PK of INC424. *In vitro*, INC424 and its M18 (main metabolite in human circulation) were not potent inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 (IC50 >25 μM for INC424 and >3 μM for M18). In addition, INC424 did not exhibit time-dependent inhibition of CYP3A4 activity or induction of CYP3A4 at clinically relevant concentrations. As the clinical steady state plasma Cmax values of INC424 and M18 following the highest proposed therapeutic dose of 25 mg twice daily are 1.2 μM and 0.14 μM, respectively, it is unlikely that INC424 or M18 at therapeutic concentrations will cause clinical drug interactions with LDE225. No transporter drug-drug interaction is expected between LDE225 and INC424 since neither is a substrate of transporters or inhibitor of transporters examined. Therefore, no drug-drug interaction is expected from the co-administration of LDE225 and INC424.

2.4 Rationale for choice of combination drugs

The rationale for the co-administration of LDE225 and INC424 is as follows:

[redacted]

- Several lines of evidence suggest that the hedgehog (Hh) signaling pathway plays an important role in many hematological malignancies.
- It has been shown that the Hh pathway is activated in MPN CD34+ cells compared to controls, as measured by Gli1 and PTCH1 expression. Also, this pathway has been shown to be activated in the MPLW515L murine model of PMF [Levine 2012].
- There is preclinical evidence that the Hh pathway is attenuated, but not eliminated, by treatment with a JAK2 inhibitor in the aforementioned PMF mouse model [Levine 2012].
- It is hypothesized that Smo inhibition might have disease-modifying effects via reduction in bone marrow fibrosis and inhibition of cancer-initiating cells.
- Potential to reduce the doses of INC424 necessary to achieve a therapeutic effect while reducing INC424-associated dose limiting toxicity (anemia and thrombocytopenia). Reduction of toxicity may allow for non-interrupted exposure to agents, bestowing a higher chance for a disease-modifying effect that may only take place upon prolonged treatment.
- Finally, no drug-drug interactions are predicted. Minimal overlapping toxicities are expected based on prior monotherapy experience for either agent. No significant myelotoxicity has been noted with the use of LDE225.

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
Phase Ib		
Primary		
To establish the MTD and/or RPIID of the co-administration of LDE225 and INC424 in patients with MF, who have not previously received therapy with a JAK inhibitor	Dose Limiting Toxicities (DLTs) occurring during the first 6 weeks of the co-administration of INC424 and LDE225	Refer to Section 10.4.
Secondary		
To evaluate the safety of the co-administration of LDE225 and INC424 in patients with MF	Adverse and serious adverse events, abnormalities in physical examinations, vital signs and laboratory test values, including ECG data	Refer to Section 10.5.1.
To characterize the single and multiple dose pharmacokinetics following the co-administration of LDE225 and INC424	LDE225 and INC424 PK parameters	Refer to Section 10.5.2.
Exploratory		
To assess the preliminary efficacy of the co-administration of LDE225 and INC424 as determined by physical examination of the spleen	Proportion of patients achieving ≥ 50% reduction in palpable spleen length measured below the left costal margin from baseline compared to Week 24	Refer to Section 10.6.
To assess the preliminary efficacy of the co-administration of LDE225 and INC424 as determined by centrally reviewed MRI/CT of the spleen at the MTD(s) and/or RPIID(s) in the expansion cohort only	Proportion of patients achieving ≥ 35% reduction in spleen volume from baseline as measured by MRI/CT at Week 24	Refer to Section 10.6.
To assess the effect of the co-administration of LDE225 and INC424 on bone marrow fibrosis by central review	Proportion of patients experiencing improvement in bone marrow fibrosis by at least one grade according to the European consensus on grading bone marrow fibrosis and assessment of cellularity (Thiele 2005) at Week 24	Refer to Section 10.6.
To assess efficacy of the co-administration of LDE225 and INC424 and the effect on disease- specific pharmacodynamic biomarkers as a function of the molecular disease characterization of MF	Efficacy parameters such as, reduction in bone marrow fibrosis and palpable spleen length from baseline compared to Week 24 Change in JAK2V617F allele burden from baseline compared to Week 24 Change in cytokine levels from baseline compared to Week 24	Refer to Section 10.6.
To assess the PK-PD relationship	Relationship of PK exposure parameters of LDE225 and INC424 with changes in safety, pharmacodynamic biomarkers and efficacy parameters	Refer to Section 10.6.

[redacted]

Objective	Endpoint	Analysis
To assess the effect of the co-administration of LDE225 and INC424 on MF-associated symptoms burden at the MTD and/or RPIID	Change from baseline in total symptom score as measured by the modified MFSAF v2.0 at Week 24 Proportion of patients having ≥ 50% reduction in total symptom score from baseline as measured by the modified MFSAF v2.0 at Week 24 Change in EORTC QLQ-C30 scores from baseline compared to Week 24	Refer to Section 10.6.
[redacted]		
Assess the effect of the co-administration of LDE225 and INC424 on Hh pathway target gene expression	Changes from baseline values in key components of the Hh pathway such as Gli1	Refer to Section 10.6.
Phase II		
Primary		
To assess the efficacy of the co-administration of LDE225 and INC424 on spleen volume reduction as determined by centrally reviewed MRI/CT	Proportion of patients achieving ≥ 35% reduction in spleen volume from baseline as measured by MRI/CT at Week 24 and Week 48	Refer to Section 10.4.
Secondary		
To assess the effect of the co-administration of LDE225 and INC424 on bone marrow fibrosis by central review and on disease-specific pharmacodynamic biomarkers as a function of the molecular disease characterization of MF	Proportion of patients experiencing improvement in bone marrow fibrosis by at least one grade according to the European consensus on grading bone marrow fibrosis and assessment of cellularity (Thiele 2005) at Week 24 and Week 48 Change in JAK2V617F allele burden from baseline compared to Week 24 and Week 48 Change in cytokine levels from baseline compared to Week 24 and Week 48	Refer to Section 10.5.
To evaluate the safety of the co-administration of LDE225 and INC424 in patients with MF	AEs, SAEs, changes in hematology and chemistry values, and assessment of physical examinations, vital signs and electrocardiograms	Refer to Section 10.5.1.
To characterize the pharmacokinetics following the co-administration of LDE225 and INC424	Stage 1: LDE225 and INC424 PK parameters Stage 2: Ctrough of LDE225 and INC424	Refer to Section 10.5.2.

[redacted]

Objective	Endpoint	Analysis
To assess the effect of the co-administration of LDE225 and INC424 on MF-associated symptoms burden	Change from baseline in total symptom score as measured by the modified MFSAF v2.0 at Week 24 and Week 48 Proportion of patients having ≥ 50% reduction in total symptom score from baseline as measured by the modified MFSAF v2.0 at Week 24 and Week 48 Change in EORTC QLQ-C30 scores from baseline compared to Week 24 and Week 48	Refer to Section 10.5.4.
Exploratory		
[redacted]		
Assess the effect of the co-administration of LDE225 and INC424 on Hh pathway target gene expression	Changes from baseline values in key components of the Hh pathway such as Gli1 at Week 24 and Week 48	Refer to Section 10.6.
[redacted]		

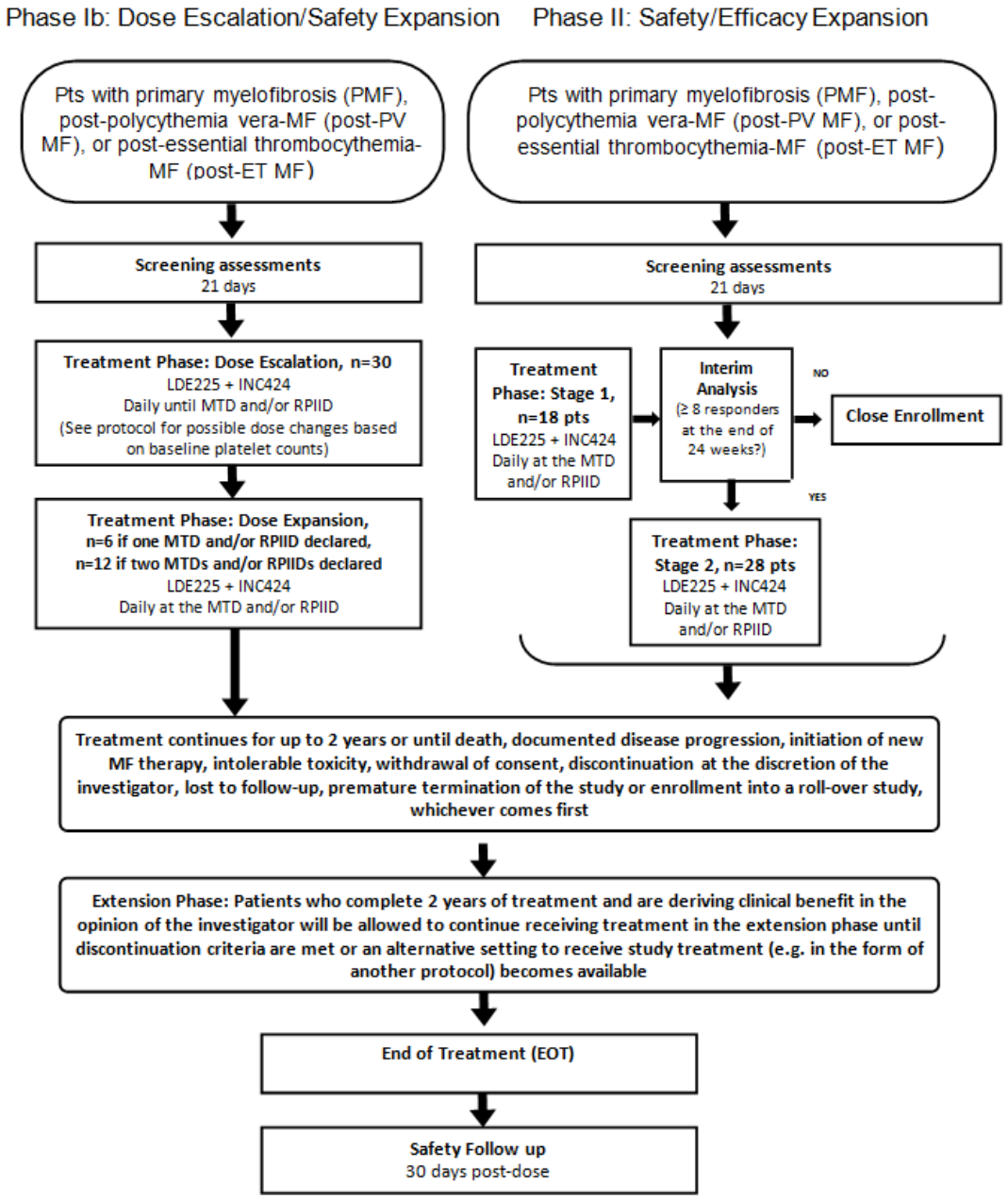
[redacted]

4 Study design

4.1 Description of study design

This study consists of an open-label, multi-center, dose-finding Phase Ib followed by an open-label, two stage, Phase II part enrolling patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (post-PV MF) or post-essential thrombocythemia myelofibrosis (post-ET MF).

Figure 4-1 Study design



4.1.1 Phase Ib dose escalation and safety expansion

Approximately five cohorts of 3-6 newly enrolled patients will receive increasing doses of LDE225 and INC424 until the MTD and/or RPIID is reached. A minimum of 3 evaluable patients are required in each cohort for making dose escalation decisions. For the purpose of dose escalation, the DLT observation period will be the first 6 weeks (42 days) following initiation of study treatment. The dose escalation part will start at 400 mg QD of LDE225 and 10 mg BID of INC424. The LDE225 dose represents 50% of the MTD and the INC424 dose represents 50% of the highest recommended starting dose when administered as monotherapy.

The minimum treatment and safety evaluation requirements for dose escalation will have been met if:

- The patient has been treated with at least 75% of the assigned treatment of LDE225 and INC424 during the first 6 weeks of study treatment (42 days) and observed for at least 6 weeks (42 days) following the first dose, and
- The patient has completed sufficient safety evaluations, as agreed by the investigators and the Sponsor, to determine whether a DLT has occurred or not.

A Bayesian Logistic Regression Model (BLRM) with overdose control (EWOC) will be used to guide dose escalation (see Section 6.2.3.2). Various dose pairs will be explored following the recommendation of an adaptive BLRM until a combination MTD and/or RPIID is determined. When enrollment of the cohort is complete, further enrollment will only resume after Novartis and the investigators have jointly reviewed the data and decided on the next dose escalation step of this combination. At each decision time point, the adaptive BLRM will provide the upper boundary for the combinations that meet the EWOC criteria. A clinical synthesis of the available toxicity information, PK, PD, and efficacy information as well as the recommendations from the Bayesian model is used to determine the combination dose for the next cohort at a dose escalation meeting or teleconference.

Each dose escalation cohort will consist of patients with low ($\leq$ 200 x10^9/L), high (> 200 x10^9/L) or both low and high baseline platelet counts. Decisions for the next dose will be made together for all patients, unless thrombocytopenia related dose limiting toxicities (DLTs) are observed, leading to different recommended dose combinations for patients with low and high baseline platelet counts. In this case, Novartis and study investigators may also decide to continue to treat both groups of patients together at the lower of the recommended dose combinations.

If a single MTD and/or RPIID is established for both low and high platelet sub-groups then an additional safety expansion cohort of 6 patients will be enrolled at that dose level to further define the safety and tolerability of the combination. If a single MTD/RPIID is established then all patients in Phase II will receive that dose irrespective of baseline platelet levels.

If separate MTDs and/or RPIIDs are declared for low and high platelet sub-groups due to differential experience relating to thrombocytopenia-related DLTs then a safety expansion cohort of 6 patients per sub-group will be enrolled and treated at the respective MTDs/RPIIDs. However, if deemed appropriate Novartis and the investigators may decide to use the lower MTD/RPIID for all patients in the Phase II portion, regardless of the baseline platelet count. Refer to Section 6.2.3.1 for the definition of the MTD and/or RPIID.

[redacted]

Approximately 36 patients are expected to participate in the dose escalation and safety expansion part. The total number of patients enrolled in the entire study will depend on the number of dose escalation steps and drop-outs.

Once the MTD and/or RPIID is established, efficacy of the oral co-administration therapy through MRI/CT scans measuring splenic volume reduction from baseline will be evaluated using a Bayesian predictive probability of success (PPOS) index during the Phase II portion of the study. In Phase II, encouraging efficacy will be concluded if the proportion of patients achieving a ≥ 35% reduction in spleen volume from baseline, as measured by MRI/CT at 24 weeks, is ≥ 50%. Additionally, in this Phase II part, the effect of the combination on bone marrow fibrosis and disease-specific pharmacodynamics biomarkers as a function of the molecular disease characterization of myelofibrosis will be evaluated. [redacted] If two MTDs/RPIIDs are established, all patients in Phase II will receive the corresponding dose based on their platelet status.

Approximately 46 patients in total will be enrolled in two stages in the Phase II part. An interim analysis will be conducted after Stage 1, see Section 4.2 for details.

Patients will continue the study treatment for at least 2 years after the first dose or until death, documented disease progression, intolerable toxicity, withdrawal of consent, discontinuation at the discretion of the investigator, lost to follow-up or discontinuation from the study, whichever comes first. Patients who complete 2 years of treatment and are deriving clinical benefit in the opinion of the investigator will be allowed to continue receiving treatment (LDE225 and INC424) in an extension phase of this study, until discontinuation reasons are met or an alternative setting to receive study treatment (e.g., in form of another protocol) becomes available.

4.2 Timing of interim analyses and design adaptations

An interim analysis will occur after 18 patients enroll into Stage 1 of the phase II part of the study and have been observed for a minimum of 24 weeks or until death, documented disease progression, intolerable toxicity, withdrawal of consent, discontinuation at the discretion of the investigator, or lost to follow-up. After this timeframe, enrollment will be halted for futility if there are less than 8 responders (i.e., patients with a spleen volumetric reduction from baseline of at least 35% by MRI/CT at 24 weeks). If at least 8 patients respond over the minimum observation period of 24 weeks, 28 additional patients will be enrolled into stage 2.

4.3 Definition of end of the study

4.3.1 End of study treatment

Patients will be treated for at least 2 years or until they permanently discontinue both study drugs due to any cause. Patients who complete 2 years of treatment and are deriving clinical benefit in the opinion of the investigator will be allowed to continue receiving treatment

[redacted]

(LDE225 and INC424) in an extension phase of this study, until discontinuation reasons are met or an alternative setting to receive study treatment (e.g., in form of another protocol) becomes available.

If either of the combination drugs is permanently discontinued then the other combination partner must also be permanently discontinued.

4.3.2 End of study

The study will end when the last patient completes treatment, or 30 days after the last patient discontinues from the study, or early termination of the study, whichever comes first.

The Clinical Study Report (CSR) will be written at the end of the trial when all patients have discontinued.

4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.1 for a discontinued or withdrawn patient. 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

Adult patients, aged ≥ 18 years who have been diagnosed with PMF, post-PV MF, or post-ET MF, as defined by the World Health Organization (2008) and:

- Are classified as high risk (3 or more prognostic factors) OR intermediate risk level 2 (2 prognostic factors) OR intermediate risk level 1 (1 prognostic factor which is not age), as defined by the International Working Group, IWG (Cervantes 2009).
- Exhibit palpable splenomegaly ≥ 5 cm below the left costal margin and MF-related active symptoms.
- Exhibit platelet counts of ≥ 75 x 10^9/L without the aid of transfusions.

Only JAK inhibitor naïve patients will be eligible for the study.

The total number of patients expected to enroll into the entire study, allowing for dropouts and non-evaluable patients, is approximately 82. The actual number of patients recruited will depend upon the number of dose levels tested in the dose escalation set, the number of patients enrolled into the safety expansion and the Phase II part.

Patients enrolled in the study cannot participate in any concurrent clinical study investigating other investigational agents or devices. Patients who have completed or discontinued the study may not be re-enrolled in the study.

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

[redacted]

5.2 Inclusion criteria

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

1. Written informed consent must be obtained prior to any screening procedures.
2. Patients must be 18 years or older.
3. Patients must be diagnosed with PMF, post-PV MF or post-ET MF, as established in the 2008 World Health Organization (WHO) criteria for PMF (Tefferi 2008), and the proposed criteria for post-PV MF and post-ET MF outlined by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) (Barosi 2008).
4. Ineligible or unwilling to undergo stem cell transplantation.
5. Platelet count $\geq 75 \times 10^9$/L not reached with the aid of transfusions.
6. ANC $> 1.5 \times 10^9$/L, without the use of G-CSF within two weeks prior to Screening.
7. INR < 1.5.
8. ECOG performance status ≤ 2.
9. Palpable splenomegaly defined as ≥ 5 cm below the left costal margin.
10. Patients must be classified as intermediate risk level 1 (1 prognostic factor which is not age), Intermediate risk level 2, or high risk. The prognostic factors, defined by the International Working Group (Cervantes 2009) are:
    - age > 65 yrs,
    - presence of constitutional symptoms (weight loss > 10% in the year preceding the Screening Visit, unexplained fever, or excessive night sweats persisting for more than 1 month),
    - marked anemia (Hgb < 10g/dL),
    - leukocytosis (history of WBC $> 25 \times 10^9$/L),
    - circulating blasts $\geq 1\%$,

      * A hemoglobin value < 10 g/dL must be demonstrated during Screening for patients who are not transfusion dependent. Patients receiving regular transfusions of packed red blood cells will be considered to have hemoglobin < 10 g/dL for the purpose of evaluation of risk factors.
11. Patients must have active symptoms of MF as demonstrated by one symptom score of at least 5 (0 to 10 point scale) or two symptom scores of at least 3 (0 to 10 point scale) on the MF Symptom Assessment Form (MFSAF).
12. Patients must have discontinued all drugs used to treat their underlying MF disease for at least 7 days prior to Screening. Corticosteroids used for conditions other than MF are allowed, as long as the daily dose is less than the equivalent of 10 mg of prednisolone, and has been stable (or decreasing) for at least 5 days before initiating study therapy.

5.3 Exclusion criteria

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

1. Previous therapy with JAK inhibitors.
2. Previous therapy with a Smo inhibitor.
3. Patients with inadequate organ function as demonstrated by:

[redacted]

- encephalopathy grade 1 or more, as per West Haven Criteria (Ferenci 2002, Appendix 6),
- known hepatocellular disease (e.g. active hepatitis or cirrhosis),
- Total bilirubin ≥ 2 x upper limit of normal (ULN) range of values, unless due to elevated indirect bilirubin (e.g. Gilbert's syndrome or hemolysis),
- alanine aminotransferase (ALT) > 3 ULN,
- MDRD eGFR < 30 mL/min/1.73m2 or on dialysis (Appendix 5),
- Creatine phosphokinase (CPK) > 1.5 x ULN.

4. Patient has impaired cardiac function or clinically significant heart disease, including any one of the following:
   - Clinically significant heart disease (e.g., congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen),
   - QTc interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males and > 470 msec for females on the screening ECG,
   - A past medical history of clinically significant ECG abnormalities or a family history of prolonged QT-interval syndrome,
   - Angina pectoris within 3 months before first dose of study treatment,
   - Acute myocardial infarction within 3 months before first dose of study treatment.
5. Patient has evidence of an active malignancy, with the exception of controlled prostate cancer, basal cell or squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast and has been disease-free for more than 3 years.
6. Patients with acute bacterial infections requiring antibiotic therapy should delay screening/enrollment until the course of antibiotics has been completed.
7. Patient is currently on medications that interfere with coagulation (including warfarin) or platelet function. Low dose aspirin (up to 150 mg per day) and low molecular weight heparin (LMWH) are allowed.
8. Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of INC424 or LDE225 (e.g., uncontrolled nausea, vomiting, diarrhea; malabsorption syndrome; small bowel resection).
9. Patient had major surgery within 2 weeks of initiation of study medications.
10. Patients who have had splenic irradiation within 12 months prior to Screening.
11. Patients who have neuromuscular disorders (e.g. inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis and spinal muscular atrophy) or are on concomitant treatment with drugs that are recognized to cause rhabdomyolysis, such as HMG CoA inhibitors (statins), clofibrate and gemfibrozil. Pravastatin may be used if necessary, with extra caution.
12. Patients who plan on embarking on new (or unaccustomed) physical activities, such as strenuous exercise, that can result in significant increases in blood CK levels while on study treatment. NOTE: As a precaution, strenuous muscular activity should be avoided for at least 1 week prior to testing for blood CK levels.

[redacted]

13. Use of other investigational drugs within 30 days of or 5 half-lives of initiation of study treatment, whichever is longer.
14. Patients who are receiving treatment with medications known to be moderate and strong inhibitors or inducers of CYP3A4/5 or drugs metabolized by CYP2B6 or CYP2C9 that have narrow therapeutic index, and that cannot be discontinued before starting treatment with LDE225. Medications that are strong CYP3A4/5 inhibitors should be discontinued at least 7 days and strong CYP3A4/5 inducers for at least 2 weeks prior to starting treatment with LDE225.
15. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
16. Patients who are not willing to apply highly effective contraception during the study and through the duration as defined below after the final dose of study treatment.
    Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and through **20 months** after the final dose of study treatment. Highly effective contraception is defined as either:
    - Total abstinence: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception,
    - Sterilization: Patient has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment,
    - Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). [For female study patients, the vasectomised male partner should be the sole partner for that patient],
    - Use a combination of the following (both a+b):
      a. Placement of a non-hormonal intrauterine device (IUD) or non-hormonal intrauterine system (IUS),
      b. Barrier method of contraception: Condom or Occlusive cap (diaphragm or cervical vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

      Note:

      i) Hormonal contraception methods (e.g. oral, injected, implanted) are not allowed as it cannot be ruled out that the study drug decreases the effectiveness of hormonal contraception.

      ii) Women are considered post-menopausal and not child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea with serum FSH levels > 40 mIU/mL and estradiol < 20 pg/mL or have had surgical bilateral oophorectomy (with or without hysterectomy) at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

[redacted]

iii) **Male patient** must use highly effective (double barrier) methods of contraception (e.g., spermicidal gel plus condom) for the entire duration of the study, and continue to use contraception and refrain from fathering a child for 6 months following the last dose of study drug. A condom is also required to be used by vasectomized men in order to prevent delivery of the study treatment via seminal fluid.

17. Inability to understand the protocol requirements, instructions and related restrictions, the nature, scope and possible consequences of the study.
18. Unlikely to comply with the protocol requirements, instructions and study related restrictions (e.g. uncooperative attitude, inability to return for follow up visits, psychological illness, and improbability of completing the study).

6 Treatment

6.1 Study treatment

In this study, the terms “investigational drug”, “study drug” or “study treatment” refers to the oral co-administration of LDE225 QD and INC424 BID administered to patients daily. The investigational treatment for this trial, which is the drug combination whose properties are being tested in this study, is LDE225 and INC424.

6.1.1 Dosing regimen

Table 6-1 Dose and treatment schedule

Study treatments	Pharmaceutical form and route of administration	Dose	Frequency and/or Regimen
LDE225	Capsule for oral use	Starting dose 400 mg to be increased or decreased per Bayesian design (see Section 6.2.1)	Once a day/QD
INC424	Tablet for oral use	Starting dose 10 mg to be increased per Bayesian design (see Section 6.2.1)	Twice a day/BID

Patients should be instructed to take their daily dose of LDE225 once in the morning and INC424 twice a day, at approximately the same time each day. Each daily dose of LDE225 (including days which involve PK blood sampling) must be taken approximately 2 hours after a light breakfast (e.g., consisting of milk, toast and jam). For example, if breakfast was completed at 08:00 a.m., then study drug administration should occur at 10:00 a.m. Patients must also then fast from food and drinks (except water) for 1 hour following dosing. A light snack may be taken if absolutely necessary (eg, crackers or toast), but high-fat meals must be avoided for 2 hours before and 1 hour after each dose. INC424 can be taken with or without food, therefore the morning dose of INC424 can be taken concurrently with LDE225. The afternoon/evening dose of INC424 can be taken with or without food, approximately 12 hours after the morning dose. LDE225 and INC424 should be taken with a glass of water and should be swallowed whole. Patients must avoid consumption of Seville (sour) oranges/ juice, grapefruit products/juice, grapefruit hybrids, pummelos and exotic citrus fruits during the

entire study and preferably 7 days before the first dose of study medications, due to potential CYP3A4 interaction with the study medications. Orange juice is allowed.

If the patient forgets to take his/ her daily LDE225 dose, then they should take it within 6 hours after the missed dosing time. If more than 6 hours have passed, then that day's dose must be omitted and the patient should continue treatment with the next scheduled dose.

If a patient misses a dose of INC424, then he/she should take INC424 within 3 hours after the missed dose. If more than 3 hours have passed, then that missed dose should be omitted and the patient should continue treatment with the next scheduled dose. Patients should not take 2 doses at the same time.

Patients should inform the investigational site staff of any missed or delayed doses.

If vomiting occurs during the course of the study treatment, then no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting must be noted in the adverse events section of the eCRF.

On days when pre-dose PK sampling is required, the patient should take his/her dose at the clinic after the sampling and a light meal. The patient must not eat until instructed to do so at the clinic.

6.1.2 Ancillary treatments

Not applicable.

6.1.3 Rescue medication

Not applicable.

6.1.4 Guidelines for continuation of treatment

For guidelines on the continuation of treatment, refer to Section 6.3 Dose modifications.

6.1.5 Treatment duration

The planned duration of treatment is at least 2 years. Patients may be discontinued from treatment with the study drugs due to documented disease progression, intolerable toxicity, withdrawal of consent, discontinuation at the discretion of the investigator, or lost to follow-up, whichever comes first. Patients who complete 2 years of treatment and are deriving clinical benefit in the opinion of the investigator will be allowed to continue receiving treatment (LDE225 and INC424) in an extension phase of this study, until discontinuation reasons are met or an alternative setting to receive study treatment (e.g., in form of another protocol) becomes available.

The extension phase will begin on the day after the Week 105 visit. The first extension phase visit will occur 12 weeks after the Week 105 visit. See Table 7-2 for the schedule of assessments during the study extension phase.

A safety follow-up will be conducted 30 days (+3 days) after the last dose of study medication is received and a study completion form will be completed in the eCRF. The safety follow-up

[redacted]

may be waived if the patient is continuing on INC424 and LDE225 treatment in an alternative setting.

6.2 Dose escalation guidelines

6.2.1 Starting dose rationale

INC424 as a single agent has been tolerated up to doses of 25 mg BID and a minimum 25% reduction in splenomegaly was seen in the majority of patients treated at 10 mg BID, 15 mg BID, and 25 mg BID (Verstovsek 2010). From [INCB018424-251] and supported by results from [CINC424A2352] (See Section 1.4.2.2.3), 15 mg BID and 20 mg BID were established as the most effective and safest starting doses followed by individualized dose titration (Verstovsek 2010).

LDE225 as a single agent has been evaluated in dose levels of 100, 200, 400, 800, 1000, 1500 and 3000 mg QD, and 250, 400 and 750 mg BID. Based on the available data from [CLDE225X2101], the maximum tolerated dose of LDE225 in adult patients is 800 mg QD. Since this is the first study of LDE225 in combination with INC424, starting doses that are lower than the respective MTDs and/or clinically approved doses have been chosen as LDE225 400 mg QD plus INC424 10 mg BID.

The starting dose and regimen are considered safe. In addition, no drug-drug interaction is expected from the combination.

The starting doses for each drug have been selected based on prior monotherapy experience where these doses have shown some degree of clinical activity as single agents and pharmacodynamic data supports the activity observed. In the interest of patient safety, both of these compounds will start at dose levels at or near 50% of their respective maximum tolerated doses. The provisional doses for dose escalation are shown in Table 6-2.

6.2.2 Provisional dose levels

The first cohort will start at low doses for both drugs (LDE225 at 400 mg QD and INC424 at 10 mg BID). The doses will then be escalated following the recommendation of an adaptive Bayesian logistic regression model for dose escalation with overdose control (EWOC) until the MTD and/or RPIID is defined.

Dose escalation will be guided by the following considerations:

- At all decision time points, the adaptive Bayesian logistic model permits alterations in the dose increments based on the observed DLTs. Only one of the 2 combination partners can be escalated and the maximum inter-cohort dose escalation is limited to 100%, i.e. up to 100% and 0% increase for LDE225 and INC424 respectively or 0% and up to 100% increase for LDE225 and INC424 respectively.
- The proposed combination meets the EWOC criteria (i.e. less than 25% chance that the true rate of DLT lies within the interval [35% - 100%].
- If at any time ≥ 35% of patients in a cohort experience a DLT and 2 or more DLTs have occurred in that cohort, one of the following actions will be implemented:
  1. Reduce the dose of one of the combination partners or both and enroll a new cohort

[redacted]

2. Termination of any further escalation of the combination partners

If two MTDs/RPIIDs are established all patients in Phase II will receive the corresponding dose based on their platelet status. The selected action may only be permitted if the respective dose combination satisfies the overdose control criteria.

Table 6-2 describes the starting dose and the dose levels that may be evaluated during this trial.

Table 6-2 Provisional dose levels

Dose level	Proposed daily dose*	Increment from previous dose
Cohort -1**	INC424 10 mg BID, LDE225 200 mg QD	-50% LDE225 dose
Cohort 1	INC424 10 mg BID, LDE225 400 mg QD	(starting dose)
Cohort 2	INC424 15 mg BID, LDE225 400 mg QD	+50% INC424 dose
Cohort 3	INC424 15 mg BID, LDE225 800 mg QD	+100 % LDE225 dose
Cohort 4	INC424 20 mg BID, LDE225 800 mg QD	+33% INC424 dose

*Depending on the emerging data, it is possible to explore other combination dose levels without exceeding the highest admissible combination dose-level per the BLRM. Thus, intermediate dose levels other than those listed above may be evaluated.
**Dose level -1 represents the treatment dose for patients requiring a dose reduction from the starting dose level. No dose reduction below dose level -1 is permitted for this study, however if patients experience thrombocytopenic DLTs in Cohort 1 then those patients will receive INC424 5 mg BID and LDE225 200 mg QD.

6.2.3 Guidelines for dose escalation and determination of MTD and/or RPIID

6.2.3.1 Definitions of MTD and/or RPIID

The MTD for this study is defined to be the highest dose of LDE225 and INC424 not expected to cause dose limiting toxicity (DLT) in more than 35% of patients.

The RPIID may be determined to be the same as the MTD or may be lower if the evolving safety profile and other assessments (e.g. PK) suggest a better safety profile without substantial loss of benefit in exposure/potential antitumor activity. The RPIID may also be determined without reaching MTD (e.g. no substantive increases in exposure with increases in dose), if evolving safety and other assessments indicate further increases in dose will result in excessive toxicity without additional benefit.

6.2.3.2 Implementation of dose escalation decisions

A 6-parameter Bayesian Logistic Regression Model (BLRM) for combination treatment will be fitted on the 6-week dose-limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose escalation to model the dose-toxicity relationship of LDE225 and INC424 when given in combination.

The general plan is that cohorts of patients will receive escalating doses of LDE225 or INC424 until the MTD of the combination is reached. Each cohort will consist of newly enrolled patients. The following provides a full description of the algorithm of dose escalation/de-escalation for the study:

a. A cohort of 3 to 6 evaluable patients will typically be treated at each dose level of LDE225 in combination with INC424.

[redacted]

b. Patients will be considered evaluable for dose escalation if they have met the minimum treatment and safety evaluation requirements listed below or if they experience a DLT during the first 6 weeks. Patients who do not meet the minimum treatment and safety evaluation requirements provided below will be regarded as ineligible for inclusion in the dose determining set (DDS: see Section 10.1.3) and additional patients may be enrolled to ensure an adequate number of evaluable patients in each cohort. The minimum treatment and safety evaluation requirements for dose escalation will have been met if:
   1. The patient has been treated with at least 75% of the planned doses of LDE225 and INC424 in 6 weeks (42 days) (i.e. no more than 10 missed doses of LDE225 and no more than 20 missed doses of INC424 in 6 weeks are permitted).
   2. The patient has been observed for at least 6 weeks following the first dose, and
   3. The patient has completed sufficient safety evaluations, as agreed by the investigators and the Sponsor, to determine that a DLT did not occur.
c. After completion of each cohort the BLRM will be used to make recommendations about the next dose level, with the following two exceptions:
   - If 2 of the first 2-3 patients in a cohort experience a DLT, further enrollment to that cohort will be suspended. The Bayesian logistic regression model will be updated with this new information before additional patients are enrolled to the study.
   - If a decision is made to escalate to a higher dose level, but one or more additional patient(s) (under the condition e) treated at any previous dose level experiences a DLT in 42 days, then the BRLM will be updated before any additional patient is enrolled to the higher dose level.
d. Following the principle of EWOC, after completion of each cohort of patients the recommended dose is one among the doses fulfilling EWOC, and typically, the one with the highest posterior probability of the DLT rate falling in the target interval [0.16, 0.35). Per EWOC it should be unlikely (< 25% posterior probability) that the DLT rate at the dose will induce excessive toxicity [0.35, 1.00]. The maximum dose increments specified in Section 6.2.2 will not be exceeded.
e. For further understanding of the safety, tolerability and PK of LDE225 and INC424, additional patients may be enrolled at dose levels established to be safe before or while proceeding with further dose escalation.

To determine the dose regimen for the next cohort, the available toxicity information (including adverse events that are not DLTs), PK, PD, and efficacy information, as well as the recommendations from the BLRM will be evaluated by the Investigators and Novartis study personnel (including the study physician and statistician) at a dose decision meeting or teleconference.

Dose escalation will continue until identification of the MTDs and/or RPIIDs. This will occur when the following conditions are met:

1. at least 9 patients have been treated at each MTD and/or RPIID dose,
2. this dose satisfies one of the following conditions:
   a. the posterior probability of targeted toxicity at this dose exceeds 50%, or
   b. a minimum of 24 patients have already been treated in Phase Ib.

[redacted]

Drug administration at the next dose level may not proceed until the investigator receives written confirmation from Novartis that the results of the previous dose level were evaluated and it is safe to proceed to a higher dose level. The Dose Determining Set (DDS: See Section 10.1.3) will be used for the determination of the MTD and/or RPIID.

6.2.4 Dose cohort modification

Provisional dose levels are listed in Table 6-2. Possible changes in dose administration according to the BLRM include but are not limited to:

a. Expansion of the current dose group to further assess suspected treatment-related adverse events
b. Administration of a dose below the starting dose for the study
c. Administration of an intermediate dose between the current and preceding dose
d. Administration of an intermediate dose between the current and the next planned dose
e. Termination of any further escalation of study drug

If a decision is made to escalate to a higher dose level, and subsequently additional patient(s) on the lower dose level experiences a DLT in the first 6 weeks of treatment, then further enrollment of patients to the higher current dose will be put on hold until the statistical model has been updated with the new safety information. Enrollment to the higher dose level may be resumed only if it is still recommended by the updated model and considered acceptable following a medical review.

Clinically relevant toxicities will be those assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications.

Additional patients may be enrolled if the minimum number of evaluable patients required to meet study objectives are not available.

6.2.4.1 Implementation of dose escalation decisions

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

6.2.4.2 Intra-patient dose escalation during Phase Ib

Intra-patient dose escalation is not permitted at any time within the first 24 weeks of study treatment. At Week 25, individual patients on INC424 doses of 10 mg or 15 mg BID may be considered for treatment at one INC424 dose level higher than the dose level to which they were initially assigned, the LDE225 dose must remain constant. Patients may only intra-patient dose escalate by one INC424 level every 4 weeks up to a maximum dose of INC424 20 mg BID. In order for a patient to be treated at a higher dose level of INC424, he or she must have tolerated the initial dose level for at least 24 weeks of therapy (e.g., he or she must

[redacted]

not have previously experienced a toxicity of CTCAE grade ≥ 2 for which relationship to study drug cannot be ruled out). Moreover, the new, higher dose level with which the patient is to be treated must be a dose level that has been declared to be well-tolerated at a dose escalation meeting and does not exceed the MTD.

Consultation with Novartis must occur prior to any intra-patient dose escalation occurring. These changes must be recorded on the Dosage Administration Record CRF.

6.2.5 Definitions of dose limiting toxicities (DLTs)

A dose-limiting toxicity (DLT) is defined as an adverse event or abnormal laboratory value assessed as unrelated to disease progression, inter-current illness, or concomitant medications that meets any of the following criteria in Table 6-3.

For the purpose of dose escalation decisions, only DLTs occurring during the first 6 weeks of study treatment will be necessarily considered and included in the BLRM.

Toxicity will be assessed using the NCI Common Terminology Criteria for Adverse Events, version 4.03 (evs.nci.nih.gov/ftp1/CTCAE) unless otherwise specified.

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

For toxicities which, by definition, require a time-window in order to be defined as DLTs (grade 3 non-hematologic toxicity for ≥ 7 consecutive days), a subsequent visit and/or laboratory assessments must be scheduled accordingly. For example, if a grade 3 non-hematologic toxicity is observed, it must also be observed at least 7 days later, with no intervening lower grades, in order to qualify as a DLT.

Table 6-3 Criteria for defining dose-limiting toxicities

TOXICITY	DLT CRITERIA
Hematologic	
Blood and lymphatic system disorders	Neutropenia CTCAE Grade 4*
	Febrile neutropenia CTCAE Grade ≥ 3 (ANC < 1.0 x 10^9/L + Fever ≥ 38.5 degrees C)
	Thrombocytopenia CTCAE Grade 4 (Platelets < 25 x 10^9/L)*
	Hemorrhagic Event CTCAE Grade ≥ 2
	Anemia CTCAE Grade 4 for ≥ 7 days despite PRBC transfusions
Non-Hematologic	
Gastrointestinal disorders	Vomiting CTCAE Grade ≥ 3 for > 7 days in duration
	Nausea CTCAE Grade 3 despite the use of anti-emetic therapy
Hepatic	Total bilirubin CTCAE Grade ≥ 3, with Direct Bilirubin ≥ 0.5 mg/dL
	AST/SGOT or ALT/SGPT CTCAE Grade 3 for ≥ 5 consecutive days AST/SGOT or ALT/SGPT CTCAE Grade 4
CK elevation	CTCAE Grade ≥ 3
Other	Any CTCAE Grade 3 non-hematologic toxicity for ≥ 7 days Any CTCAE Grade 4 non-hematologic toxicity
CTCAE version 4.03 will be used for all grading. * In two consecutive assessments (the second assessment will be considered valid and final)	

[redacted]

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol.

Patients who experience a DLT will have their therapy with LDE225 and INC424 interrupted and will be followed as described in Table 6-4. After recovery from the toxicity in question, if the Investigator believes that it is in the patient's best interest to resume therapy with LDE225 and INC424, the patient may resume therapy, only after consultation with the Sponsor, according to the guidelines described in Section 6.3.1 and Table 6-4.

However, the patient must be permanently discontinued from study medication and withdrawn from the study, if any of the following DLTs occur:

- any grade ≥ 3 hemorrhagic event
- grade 4 anemia for ≥ 7 consecutive days despite PRBC transfusions
- 2nd episode of grade ≥3 febrile neutropenia
- grade 3 renal toxicity for ≥ 7 consecutive days
- grade 4 renal toxicity
- grade 4 non-hematologic toxicity

If during the first 6 weeks a patient misses > 10 doses of LDE225 or > 20 doses of INC424, the patient will not be evaluable for DLTs. The patient can continue in the study, but another patient has to be enrolled at the same dose level in order to reach the required minimum number of patients in the cohort.

6.2.5.1 Follow-up for dose-limiting toxicities

Patients whose treatment is discontinued or interrupted due to a DLT, must be followed until resolution or stabilization of the DLT event, whichever comes first, as described in Section 6.3.1.

In case of a hemorrhagic event, of any grade (CTCAE grade 1 included), the Investigator is advised to perform coagulation tests and an albumin assessment.

Additional guidance on the management of grade 4 thrombocytopenia and grade 4 neutropenia is described in Section 6.3.2.

6.3 Dose modifications

6.3.1 Dose modification and dose delay

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied. Any plan to deviate from these guidelines in view of patient safety must be discussed with the sponsor unless there is an urgent need for action.

All dose modifications should be based on the worst preceding toxicity as graded by the NCI Clinical Toxicity Criteria (NCI-CTCAE version 4.03). If study treatment is held due to toxicity, scheduled visits and all assessments as described in Table 7-1 should continue as scheduled, except without dosing. Dose modification guidelines are described in Table 6-4.

[redacted]

If an adverse event is clearly associated to one of study drugs, the dose adjustment directed for that study drug will be followed; however, if the causality is not clear, then it may be necessary to adjust both study drugs. Dosing adjustments will be discussed with the sponsor.

If a patient experiences a DLT then treatment with LDE225 plus INC424 must be stopped and the patient may be discontinued from the study. However, following resolution of the DLT to CTCAE grade 1 or to the patient's baseline value, the patient may continue to receive study treatment at a reduced combination dose level, if appropriate, at the discretion of the investigator and after discussion with the Sponsor.

For each patient, a maximum of 2 dose reductions will be allowed, after which the patient will be required to discontinue study treatment. If the same toxicity returns after re-initiation of treatment at the same dose level, the second re-initiation must resume at a lower dose level. The patient must also discontinue study treatment if, after the treatment is resumed at the lower dose level, the same toxicity recurs with the same or worse severity (except for thrombocytopenia, anemia and neutropenia).

Dose level (-1) is the lowest acceptable dosing level for a patient participating in the study. If a patient cannot tolerate dose level (-1), then study treatment must be discontinued and the patient must be withdrawn from the study. However, if patients in Cohort 1 experience thrombocytopenic DLTs then patients in dose level (-1) will receive INC424 5mg BID and LDE225 200 mg QD.

If a patient requires a dose delay from either study drug of > 21 days due to an LDE225 or INC424 related toxicity, then the patient must be discontinued from the study; however, if the patient is obtaining clinical benefit in terms of response, the patient may continue treatment at the same or at a reduced dose following discussion between the investigator and Novartis. All patients will be followed for AEs and SAEs for 30 days following the last dose of LDE225 and/or INC424.

Dose modifications for toxicities occurring during the DLT-definition period (6 weeks or 42 days) will not be allowed unless the toxicity qualifies as a DLT. After a toxicity has been characterized as a DLT, a patient can resume therapy with a reduced treatment dose according to the guidelines provided in Section 6.2.5.1.

If the administration of study treatment was interrupted for reasons other than toxicity, then treatment with LDE225 and INC424 may be resumed at the same dose.

Patients who experience muscle toxicity, regardless of whether the toxicity meets the criteria described for a DLT, should be followed according to the dosing modifications for LDE225 as per Table 6-5.

Patients who experience hematologic, renal, or hepatic toxicities should receive follow up evaluations as outlined in Table 6-7.

All interruptions or changes to study drug administration must be recorded on the Dosage and Administration Record eCRF.

[redacted]

Table 6-4 Criteria for interruption and re-initiation of INC424 and LDE225 treatment

Dose modifications for toxicities occurring during the DLT-definition period (6 weeks or 42 days), and considered as treatment-related, will not be allowed until the toxicity qualifies as a DLT.	
Worst toxicity (CTCAE 4.03 Grade)	Dose Modifications for INC424 and LDE225
HEMATOLOGICAL	
Neutropenia (ANC) (for 2 consecutive assessments within 48 hrs except febrile neutropenia)	
Grade 1 (ANC < LLN - 1.5 x 10^9/L) Grade 2 (ANC < 1.5 - 1.0 x 10^9/L) Grade 3 (ANC < 1.0 - 0.5 x 10^9/L)	INC424: Maintain dose level LDE225: Maintain dose level
Grade 4 (ANC < 0.5 x 10^9/L)	INC424: Hold dose until resolved to ≤ grade 1, then maintain dose level LDE225: Hold dose until resolved to ≤ grade 1, then maintain dose level
Febrile neutropenia (Grade ≥ 3) (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)	INC424: Discontinue study treatment LDE225: Discontinue study treatment
Thrombocytopenia (for 2 consecutive assessments within 48 hrs)	
Grade 1 (PLT < LLN - 75 x 10^9/L)	INC424: Maintain dose level LDE225: Maintain dose level
Grade 2 (PLT < 75 - 50 x 10^9/L)	INC424: Reduce to 10 mg BID or continue at same dose level (whichever is lower) LDE225: Maintain dose level
Grade 3 (PLT < 50-25 x 10^9/L)	INC424: Reduce to 5mg BID LDE225: Maintain dose level
Grade 4 (PLT < 25 x 10^9/L)	INC424: Hold dose until resolved to ≤ grade 1, then maintain dose level LDE225: Hold dose until resolved to ≤ grade 1, then maintain dose level
Hemorrhagic event of any kind (if related to study treatment)	
Grade 1	INC424: Maintain dose level LDE225: Maintain dose level
Grade 2	INC424: Hold dose until resolved completely, then ↓ by 5 mg BID LDE225: Hold dose until resolved completely, then maintain dose level
Grade 3 or 4	INC424: Discontinue study treatment LDE225: Discontinue study treatment
RENAL	
Serum creatinine	
< 2 x ULN	INC424: Maintain dose level LDE225: Maintain dose level
2 – 3 x ULN	INC424: Hold dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ by 5 mg BID LDE225: Hold 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 – 6.0 x ULN)	INC424: Discontinue study treatment LDE225: Discontinue study treatment
Grade 4 (> 6.0 x ULN)	INC424: Discontinue study treatment LDE225: Discontinue study treatment

[redacted]

Dose modifications for toxicities occurring during the DLT-definition period (6 weeks or 42 days), and considered as treatment-related, will not be allowed until the toxicity qualifies as a DLT.	
Worst toxicity (CTCAE 4.03 Grade)	Dose Modifications for INC424 and LDE225
HEPATIC	
Bilirubin (*for patients with Gilbert Syndrome these dose modifications apply to changes in direct bilirubin only). Bilirubin will be fractionated if elevated	
Up to 2.0 x ULN	INC424: Maintain dose level LDE225: Maintain dose level
> 2.0 – 3.0 x ULN with ALT or AST ≤ 3.0 x ULN	INC424: Hold dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ by 5 mg BID LDE225: Hold dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose If resolved in > 7 days, then ↓ 1 dose level
> 3.0 - 10.0 x ULN with ALT or AST ≤ 3.0 x ULN	INC424: Hold dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then discontinue treatment LDE225: Hold dose until resolved to ≤ grade 1, then ↓ 1 dose level
> 10.0 x ULN	INC424: Discontinue study treatment LDE225: Discontinue study treatment
AST or ALT	
Grade 1 (> ULN – 3.0 x ULN)	INC424: Maintain dose level LDE225: Maintain dose level
Grade 2 (> 3.0 - 5.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	INC424: Maintain dose level LDE225: Maintain dose level
Grade 3 (> 5.0 - 20.0 x ULN) without total bilirubin elevation to > 2.0 x ULN	INC424: Hold dose until resolved to ≤ grade 1, then: If resolved in ≤ 7 days, then maintain dose level If resolved in > 7 days, then ↓ by 5 mg BID LDE225: Hold dose until resolved to ≤ grade 1, then ↓ 1 dose level
Grade 4 (> 20.0 x ULN) without bilirubin elevation to > 2.0 x ULN	INC424: Hold dose until resolved to ≤ grade 1, then ↓ by 5 mg BID LDE225: Hold dose until resolved to ≤ grade 1 or baseline, then ↓ 1 dose level
CARDIAC	
Cardiac – QTc prolongation	
QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs	Perform an analysis of serum potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. Perform a repeat ECG within one hour of the first QTcF of > 500 ms If QTcF remains > 500 ms, repeat ECG as clinically indicated but at least once a day until the QTcF returns to < 480 ms. INC424: Hold dose until QTcF prolongation has resolved, then ↓ by 5 mg BID LDE225: Hold dose. Once QTcF prolongation has resolved, study treatment may be restarted at ↓ 1 dose level Second Occurrence: Discontinue patient from further study treatment with both medications
Other non- hematological adverse events	
Grade 1 or 2	INC424: Maintain dose level LDE225: Maintain dose level

[redacted]

Dose modifications for toxicities occurring during the DLT-definition period (6 weeks or 42 days), and considered as treatment-related, will not be allowed until the toxicity qualifies as a DLT.	
Worst toxicity (CTCAE 4.03 Grade)	Dose Modifications for INC424 and LDE225
Grade 3	INC424: Hold dose until resolved to ≤ grade 1, then ↓ by 5 mg BID LDE225: Hold dose until resolved to ≤ grade 1, then ↓ by 1 dose level
Grade 4	INC424: Discontinue study treatment LDE225: Discontinue study treatment
Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Hold dose for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic. If the investigator deems that a recommended dose reduction or the recommendation to maintain the same dose is not in the best interest of the patient, this decision may be discussed with Novartis on a case-by-case basis.	

Table 6-5 Recommended LDE225 dose modifications and dose delays for suspected treatment-related muscle toxicities

Severity of CK elevation	**Dose modifications and management recommendations**
Asymptomatic CK elevation	
Grade 2 [CK elevation >2.5 x ULN - 5 x ULN]	● Continue treatment on the same dose and monitor CK levels weekly until resolution to baseline level. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.
Symptomatic (new-onset or worsening of pre-existing muscle symptoms such as myalgia, myopathy, and/or spasms) CK elevation	
Grade 1 [CK elevation >ULN - 2.5 x ULN)]	● Continue treatment at the same dose and monitor CK levels weekly until resolution to baseline level and then monthly thereafter. Monitor muscle symptoms for changes until resolution to baseline. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.
Grade 2 [CK elevation >2.5 x ULN - 5 x ULN]	● Interrupt treatment and monitor CK levels weekly until resolution to baseline level. Monitor muscle symptoms for changes until resolution to baseline. Upon resolution, resume treatment at the reduced dose level and measure CK monthly thereafter. Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated.
Asymptomatic or Symptomatic CK elevation	
Grade 3 or 4 without renal impairment [Grade 3 (CK elevation >5 x ULN - 10 x ULN)] [Grade or 4 (CK elevation >10 x ULN)]	● Interrupt treatment and monitor CK levels weekly until resolution to baseline level. Monitor muscle symptoms for changes until resolution to baseline. ● Check renal function (serum creatinine) regularly and ensure that patient is adequately hydrated. If renal function is not impaired (normal serum creatinine) and CK resolves to baseline level, consider resuming treatment at a reduced dose. CK levels should be measured weekly for 2 months after re-administration of sonidegib and monthly thereafter.
Grade 3 or 4 with renal impairment	● Interrupt treatment and monitor CK levels weekly until resolution to baseline level. Monitor muscle symptoms for changes until resolution to baseline. ● If renal function is impaired (≥50% above the baseline level), interrupt treatment. Ensure patient is adequately hydrated and evaluate other secondary causes. Continue monitoring of CK and creatinine levels weekly. If CK levels return to baseline level and creatinine levels return to baseline, consider resuming treatment at the reduced dose otherwise discontinue treatment permanently.

[redacted]

Table 6-6 Dose restart guidelines and allowed maximum doses for patients who have previously interrupted dose for grade 4 thrombocytopenia and grade 4 neutropenia

Current PLT Count	**▼ Dose Restart or Dose Increase Guidelines ▼**	
	INC424	**LDE 225**
< 50 x10^9/L	Continue to hold	Continue to hold
50 to < 75 x10^9/L	Restart at 5 mg BID for at least 14 days If stable, may increase to 10 mg BID or original dose (whichever is lower)	Restart at original dose level
75 to < 100 x10^9/L	Restart at 10 mg BID for at least 14 days If stable, may increase to 15 mg BID or original dose, (whichever is lower)	Restart at original dose level
100 to < 125 x10^9/L	Restart at original dose	Restart at original dose level
≥ 125 x10^9/L	Restart at original dose	Restart at original dose level
Current ANC Level	**▼ Dose Restart or Dose Increase Guidelines ▼**	
< 0.5 x10^9/L	Continue to hold	Continue to hold
0.5 to < 0.75 x10^9/L	5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID or original dose, (whichever is lower)	Restart at original dose level
0.75 to <1 x10^9/L	10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID or original dose, (whichever is lower)	Restart at original dose level
1 to < 1.5 x10^9/L	Restart at original dose	Restart at original dose level
≥ 1.5 x10^9/L	Restart at original dose	Restart at original dose level

6.3.1.1 Optional dose tapering strategy for INC424 in the event of discontinuation

When INC424 therapy is stopped, return of constitutional symptoms associated with elevated cytokines (e.g. night sweats, fever, fatigue) that had been suppressed while on therapy is expected. When a decision is made to permanently discontinue INC424 therapy for reasons other than for hematologic safety, a dose tapering strategy may be considered, based on evaluation of the condition of the patient, current dosing regimen and the clinical judgment of the Investigator, so that symptoms may return to pre-treatment condition more slowly. If considered to be medically necessary, the Investigator may use any treatment to manage withdrawal from INC424 including a gradual tapering of the study drug dosage or use of other medications to manage events occurring after discontinuation. Short-term courses of corticosteroids at doses > 10 mg/day have been used in patients with MF and may be considered as part of a tapering strategy. Corticosteroids may be started prior to, or concurrent with, INC424 tapering. When a decision has been made to discontinue the patient with utilization of a tapering strategy, regardless of the use of concomitant medications, safety data will continue to be assessed in accordance with the protocol for a period of time as least through the continued administration on INC424 and 30 days after for AEs.

6.3.2 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value, must be followed up at least once a week (or more

[redacted]

frequently if required by institutional practices, or if clinically indicated) for 4 weeks, and subsequently at approximately 4-week intervals, until resolution or stabilization of the event, whichever comes first. Appropriate clinical specialists should be consulted as deemed necessary. Further guidelines and recommendations for the management of specific study drug combination induced toxicities (thrombocytopenia and neutropenia) are provided in Section 6.3.2.1 and Section 6.3.2.2. All patients must be followed up for adverse events and serious adverse events for 30 days following the last dose of LDE225 and/or INC424.

Table 6-7 Follow-up evaluations for selected toxicities

Toxicity	Follow-Up Evaluation
Hematology	If any hematological DLT has occurred, the relevant parameters must be repeated at least twice a week until resolution to ≤ CTCAE grade 1, and then at least weekly until either initiation of treatment or until stabilization.
Renal	If any renal DLT has occurred, the relevant parameters must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline, and then at least weekly until either initiation of re-treatment or until stabilization.
Hepatic	If any hepatic DLT has occurred, the relevant parameters must be repeated at least twice a week until resolution to ≤ CTCAE grade 1 or baseline, and then at least weekly until either initiation of re-treatment or until stabilization. Patients with total bilirubin > ULN (any duration) should have fractionation of bilirubin into total/direct or indirect/direct components and any additional assessments as clinically indicated by these results.
Non-laboratory	Patients who experience non-laboratory DLTs must be evaluated at least once a week following demonstration of the toxicity until resolution of the toxicity, to allow for retreatment, until stabilization of the toxicity, or EOT.
Cardiac	If ≥ grade 3 (QTcF > 500 msec as identified by the investigator on the ECG reading or >60 ms change from baseline on at least 2 separate ECGs taken within 1 hour): The patient must be hospitalized or monitored by the investigators with hourly ECGs until the QTcF is ≤ 500 msec and < 30 msec from baseline. Immediate attention to potassium and magnesium and other clinical factors such as oxygenation, ischemia, and the like will be addressed. A plasma sample should be drawn to assess the concentration of LDE225, magnesium and potassium at the time when the absolute QTcF > 500 msec. Once QTcF prolongation has resolved, reinitiate treatment according to Table 6-4 and perform ECG monitoring weekly. If the ECGs obtained in the first 6 weeks after dose reduction are without any QTcF > 500 msec and QTcF change from baseline ≥ 60 msec, then ECG monitoring should be performed every 4 weeks.

6.3.2.1 Management of thrombocytopenia

It is recommended that patients who are dose reduced for thrombocytopenia have more frequent hematology assessments. Platelet counts must be obtained at least weekly for 4 weeks, and then at least every second week for the next 4 weeks. Thereafter, they may resume normal scheduled evaluations.

Dose escalation guidelines which allow maximum doses for patients who have previously decreased dosing for thrombocytopenia are described in Table 6-6.

In the case of grade 4 thrombocytopenia, assessment of platelet count is recommended to be repeated twice weekly, until resolution to grade ≤ 3 thrombocytopenia.

Dose restart guidelines and allowed maximum doses for patients who have previously interrupted dose for grade 4 thrombocytopenia can be found in Table 6-6.

[redacted]

6.3.2.2 Management of neutropenia

In the case of grade 4 neutropenia, assessment of ANC count is recommended to be repeated at least twice a week until resolution to grade ≤ 3 neutropenia.

Dose restart guidelines and allowed maximum doses for patients who have previously interrupted dose for grade 4 neutropenia can be found in Table 6-6.

6.3.3 Anticipated risks and safety concerns of the study drug

Appropriate eligibility criteria and specific DLT definitions, as well as specific dose modification and stopping rules are included in this protocol. Refer to preclinical toxicity and or clinical data found in the [LDE225 and INC424 Investigator's Brochures].

6.4 Concomitant medications

6.4.1 Permitted concomitant therapy

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 (other than study drug) and significant non-drug therapies (including physical therapy and herbal/natural medications) administered during the study must be listed on the Concomitant Medications or the Surgical and Medical procedures eCRF. Blood Transfusions will be recorded on the Blood component transfusion eCRFs.

6.4.2 Permitted concomitant therapy requiring caution and/or action

Patients receiving these medications listed below must be monitored closely for any potentiation of toxicity or decrease of clinical benefit due to any individual concomitant medications, and may require dose adjustment.

6.4.2.1 Breast cancer resistance protein (BCRP)

LDE225 is an inhibitor of breast cancer resistance protein (BCRP) *in vitro*. Therefore substrates, especially those with a narrow therapeutic range, should be used with caution. BCRP substrates include zidovudine, pantoprazole, cimetidine, sulfasalazine, nitrofuratoin, mitoxantrone, methotrexate, topotecan, imatinib, and irinotecan. However, the use of mitoxantrone, methotrexate, topotecan, imatinib, irinotecan or statins is generally prohibited during this study (see Appendix 1; Table 14-1).

6.4.2.2 Drugs that are metabolized by or affect CYP450 enzymes

In vitro drug metabolism studies suggest that the metabolism of LDE225 and INC424 are both primarily mediated by CYP3A4. Therefore, caution is advised for co-administration of drugs that are weak inhibitors or inducers of CYP3A4 (Appendix 1; Table 14-2). Concomitant treatment with weak inducers of CYP3A4 is permitted, however, duration of concomitant treatment should be kept as short as possible (e.g, less than 1 week), or fully avoided whenever possible. Weak inducers include, but are not limited to armodafinil, nevirapine, oxcarbazepine, pioglitazone, pleconaril, rufinamide and troglitazone. Note that

[redacted]

coadministration of study drug with strong and moderate CYP3A inducers (Appendix 1) is prohibited.

LDE225 was shown to inhibit CYP2B6 and CYP2C9 *in vitro*, therefore, CYP2B6 and CYP2C9 substrates should be used in caution. Refer to Table 14-3 in Appendix 1 for a list of CYP2B6 and CYP2C9 substrates to be used with caution. Narrow therapeutic index or sensitive substrates of CYP2B6 and CYP2C9 are not permitted (refer to the prohibited section below).

6.4.2.3 Corticosteroids

Chronic dosing of corticosteroids (e.g. dexamethasone and prednisone) is known to induce CYP3A enzymes, thereby increasing the risk of reducing drug exposure to sub-therapeutic levels. Systemic corticosteroid doses greater than the equivalent of 10 mg of prednisolone per day are not permitted, unless its use is part of a INC424 dose tapering strategy (Section 6.3.1.1) as this may impact splenic size and cytokine reduction and interfere with the ability to assess the clinical activity of this drug treatment combination in this patient population. Stable corticosteroids used for conditions other than MF are allowed if the doses are less than the equivalent of 10 mg of prednisolone per day during the course of the study but the dose must have been stabilized (or decreasing) for at least 5 days before initiating study therapy and any ongoing corticosteroid use during study treatment must be clearly documented on the concomitant medication eCRF.

6.4.2.4 Permitted antifungal and antibiotic medications

Permitted antifungal and antibiotic agents, including those that are weak inhibitors or inducers of CYP3A4 are listed in Appendix 1, Table 14-4. Topical and vaginal antifungals are generally allowed with caution.

6.4.2.5 Hematopoietic growth factors

Therapeutic use of hematopoietic growth factors is allowed according to institutional guidelines. Granulocyte growth factors (G-CSF) are not allowed while study medication is being administered but may be used for severe neutropenia at the Investigator's discretion while study medication is being withheld.

6.4.3 Prohibited concomitant therapy

The following medications have restrictions on their use and may require changes in dosing when INC424 and/or LDE225 are administered during the study. Refer to Appendix 1 for a list of prohibited medications. This list may not be comprehensive.

6.4.3.1 Other investigational therapies

Use of any other investigational medication (other than LDE225 and INC424) that is not approved for any indication is not allowed. Use of such medications within 30 days, prior to the first dose of study drug and during the study through the Safety Follow-up Visit is prohibited. Anticancer therapy (chemotherapy, biologic or radiation therapy, and surgery) other than the study treatments (LDE225 and INC424) must not be given to patients while the

patient is on the study medication. If such agents are required for a patient then the patient must be discontinued from the treatment portion of the study.

6.4.3.2 Strong and moderate CYP3A4 inhibitors and inducers

In vitro drug metabolism studies suggest that the metabolism of LDE225 and INC424 are both primarily mediated by CYP3A4. Co-administration with strong and moderate CYP3A4 inhibitors and inducers is predicted to respectively increase or decrease the systemic exposure to the study drugs (Appendix 1; Table 14-5), and is therefore prohibited.

6.4.3.3 Narrow therapeutic index or sensitive substrates of CYP2C9 and CYP2B6

Because of the potential risk for drug-drug interactions with LDE225, using concomitant medications known to be metabolized by the cytochromes CYP2C9 and CYP2B6 that have low therapeutic index is not permitted in the study (Appendix 1; Table 14-6). In the absence of clinical drug interaction data, therapeutic doses of warfarin or any other Coumadin-derivative anticoagulants are not permitted since LDE225 is a competitive inhibitor of CYP2C9 based on the in vitro data.

6.4.3.4 Drugs that interfere with coagulation or inhibit platelet function

Drugs that interfere with coagulation or inhibit platelet function (including non-steroidal anti-inflammatory drugs) are not permitted. Aspirin (≤ 150 mg/day) and LMWH (INR less than 1.5) are allowed.

Any other medication for the treatment of myelofibrosis, including but not limited to:

hydroxyurea, busulfan, interferon, lenalidomide, thalidomide, anagrelide **are prohibited**.

6.4.3.5 Drugs with a known risk of myopathy and rhabdomyolysis

Selected drugs that may increase risk of myopathy and rhabdomyolysis when used concomitantly with LDE225 should be avoided. Such drugs should be discontinued for at least 2 weeks prior to initiation of LDE225 and it must be ensured that plasma creatine kinase (CK) is within the normal range at screening.

6.4.3.6 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 must stop using these herbal medications at least 7 days prior to first dose of study treatment.

6.4.3.7 Prohibited antifungal and antibiotic medications

Antifungal and antibiotic agents that are moderate/strong inhibitors or inducers of CYP3A4 are prohibited due to the potential to affect the PK of LDE225 and INC424 (see Appendix 1; Table 14-7).

[redacted]

6.4.3.8 Anti-virus vaccines and medications

Live anti-virus vaccines such as Zostavax® are prohibited given INC424's potential for causing immunosuppression. Other anti- herpes virus medications such as acyclovir, gancyclovir, valacyclovir should be used with caution especially if Zoster reactivation continues to increase over time during the course of the study. Other antivirus medications which are strong and moderate inhibitors of CYP3A4 are also prohibited.

6.5 Patient numbering, treatment assignment or randomization

6.5.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient ID), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient Number 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. The procedures for obtaining a Patient Number will be provided in a separate instructional document prior to study start. Once assigned, the Patient Number must not be reused for any other patient and the Patient Number for that individual must not be changed.

6.5.2 Treatment assignment or randomization

Patients will not be randomized; the assignment of a patient to a particular cohort in the Phase Ib part of the study will be coordinated by the sponsor. The procedures for obtaining a patient number will be provided in a separate instructional document prior to study start.

6.5.3 Treatment blinding

This is an open-label study, treatment blinding is not applicable.

6.6 Study drug supply

6.6.1 Study drug preparation and dispensation

Study medication will be dispensed by an authorized person at the investigator's site. Patients will be provided with an adequate supply of study drug for self-administration at home, including instructions for administration, until at least their next scheduled study visit. Patients will receive LDE225 and INC424 study treatment on an outpatient basis. The investigator shall provide the patient with instructions for study treatment administration according to the protocol.

All dosages prescribed to the patient and all dose changes and/or missed doses during the study must be recorded on the Dosage Administration Record eCRF.

When possible, individual doses will consist of the minimum number of capsules/tablets equaling the total dose given the available capsule/tablet sizes.

[redacted]

Table 6-8 Preparation and dispensing

Study treatments	Dispensing	Preparation
LDE225	Continuous daily QD dosing	Not applicable
INC424	Continuous daily BID dosing	Not applicable

6.6.2 Study drug packaging and labeling

6.6.2.1 LDE225

LDE225 capsules will be packed and labeled by Novartis Drug Supply Management. LDE225 is formulated as capsules of 50mg, 100mg, 200mg, and 250mg strengths. Not all of the strengths listed may be used in this study. The capsules are packaged in bottles. LDE225 will be administered orally once a day.

Medication labels will conform to local legal requirements. Patient number will be added by the site pharmacist or authorized site personnel. The storage conditions for study drug will be described on the medication label.

6.6.2.2 INC424 (ruxolitinib)

INC424 tablets can be provided as local commercial material or global supply where appropriate and as per local regulations. Global supply will be open-label, packed and labeled by Novartis Drug Supply Management. Study treatment labels will be in the local language and will comply with the legal requirements of each country. Patient number will be added by the site pharmacist or authorized site personnel. The storage conditions for study drug will be described on the medication label.

INC424 tablets are formulated in strengths of 5mg, 10mg, 15mg and 20mg. INC424 in different formulations and strengths can be used once they are approved and marketed. INC424 will be administered orally twice a day.

If INC424 is sourced and labeled in-country, the locally approved form and packaging of INC424 will be used. When INC424 tablets are packaged in bottles they will be supplied in HDPE bottles with a plastic child resistant closure. These bottles must be kept out of the reach and sight of children.

Refer to the latest [INC424 Investigator's Brochure] for dosing instructions and storage conditions.

Table 6-9 Packaging and labeling

Study treatments	Packaging	Labeling (and dosing frequency)
LDE225	Capsules in bottles	Refer to study treatment label Once daily
INC424	Global supply: Tablets in bottles Locally sourced supply: Locally approved form and packaging	Refer to study treatment label Twice daily

6.6.3 Drug supply and storage

The study drugs must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the pharmacist or authorized

[redacted]

site personnel have access. Upon receipt, the investigational drugs should be stored according to the instructions specified on the drug labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Investigational drug (LDE225 and INC424) global supply will be provided by Drug Supply Management, Novartis. Local commercial material will be provided by each local Country Pharmaceutical Organization (CPO). Please refer to study treatment label for storage instructions.

The investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the field monitor during site visits and/or at the completion of the study. All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the investigator must not destroy any drug labels, or any partly used or unused drug supply. Only after receiving written authorization by Novartis, the investigator will be instructed to either send all of the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction or to dispose of unused drug according to local regulations.

Table 6-10 Supply and storage of study treatments

Study treatments	Supply	Storage
LDE225	Centrally supplied by Novartis	Refer to study treatment label
INC424	Centrally supplied by Novartis or Locally supplied by the CPO	Refer to study treatment label

6.6.4 Study drug compliance and accountability

6.6.4.1 Study drug compliance

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit. On PK sampling days, compliance will also be assured by administrations of the study treatment under the supervision of investigator or his/her designee.

6.6.4.2 Study drug accountability

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

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

[redacted]

6.6.4.3 Handling of other study treatment

Not applicable.

6.6.5 Disposal and destruction

The study drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate. Study drug destruction at the investigational site will only permitted if authorized by Novartis in a prior agreement and if permitted by local regulations.

7 Visit schedule and assessments

7.1 Study flow and visit schedule

Table 7-1 and Table 7-2 (Extension Phase) lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation.

For Table 7-1, the following visit windows will be allowed: +/- 1 day during the first 8 weeks (except Week 1 Day 1 and Week 1 Day 2), +/- 2 days during Weeks 9-13 and +/- 3 days from Week 17 onwards. Imaging has an allowable window of +/- 1 week (the window for the baseline, Week 1 Day 1, scan is -1 week) and the collection of the bone marrow biopsy and aspirate has an allowable window of +/- 2 weeks (the window for the baseline, Week 1 Day 1, bone marrow biopsy and aspirate is -2 weeks).

For Table 7-2, the following visit windows will be allowed: +/- 4 weeks for study visits and assessments, including imaging, bone marrow biopsy and aspirate.Standard of care (SOC) visits and assessments should be performed as per local treatment practices and Investigator discretion. Patient information from SOC assessments should be entered into the eCRF only if it is clinically relevant to the study treatment.

[redacted]

Table 7-1 Visit evaluation schedule

Week	Category	Protocol Section	Screening Phase	Treatment Phase												Follow up Phase	
				Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9		Week 11	Week 13 Day 1 and every 4 weeks until Week 105 Day 1	End of treatment (EOT) – if before extension phase	Follow Up/Study Completion
Study Day			-21 to -1	1	2	1	1	1	1	1	1	1	1	2	1	1	Date of last dose	30 days post-dose
Obtain Informed Consent	D	7.1.1.	X															
Patient history																		
Demography	D	7.1.1.2.	X															
Inclusion/exclusion criteria	S	7.1.1 and 5.2/5.3.	X															
Relevant medical history/current medical conditions	D	7.1.1.2.	X															
Diagnosis of PMF, P-PV MF, or P-ET MF	D	7.1.1.2.	X															
Cytogenetics	D	7.1.1.2.	X															
Prognostic factors for MF	D	7.1.1.2.	X															
Prior antineoplastic medications, radiation therapy, or prior surgery	D	7.1.1.2.	X															
Prior Medical and Surgical procedures	D	7.1.1.2.	X															
Prior and current concomitant medications/significant non-drug therapies	D	7.1.1.2 and 6.4.1.	Record prior significant medications up to 30 days before Screening Record current medications/therapies at each visit through 30 days post last dose of study treatment															
[redacted]																		
Measurement of spleen by Palpation	D	7.2.1.1.	X	X			X		X		X		X			X	X	
Physical examination	S	7.2.2.1.	X														X	

[redacted]

Week	Category	Protocol Section	Screening Phase	Treatment Phase													Follow up Phase	
				Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9		Week 11	Week 13 Day 1 and every 4 weeks until Week 105 Day 1	End of treatment (EOT) – if before extension phase	Follow Up/Study Completion
Study Day			**-21 to -1**	**1**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**Date of last dose**	**30 days post-dose**
Abbreviated Physical	S	7.2.2.1.							X				X			X		
ECOG Performance status	D	7.2.2.4.	X	X					X				X			X	X	
Height	D	7.2.2.3.	X															
Weight	D	7.2.2.3.	X				X		X		X		X			X	X	
Vital signs	D	7.2.2.2.	X	X			X		X		X		X			X	X	
Laboratory assessments																		
Phase Ib patients ONLY Hematology/Chemistry	D	7.2.2.5.1 and 7.2.2.5.2.	X	X		X	X	X	X	X	X	X	X		X	X	X	
Phase II patients ONLY Hematology/Chemistry	D	7.2.2.5.1 and 7.2.2.5.2.	X	X			X		X		X		X		X	X	X	
CK	D	7.2.2.5.3.	X	X			X		X		X		X		X	X	X	
Coagulation (INR and PTT)	D	7.2.2.5.4.	X	X					X				X			X	X	
Urinalysis	D	7.2.2.5.5.		X	As clinically indicated												X	
Pregnancy Serum test (women of childbearing potential only)	D	7.2.2.5.6.	X (to be done ≤ 7days prior to first dose)														X	
Pregnancy Urine test (women of childbearing potential only)	D	7.2.2.5.6.							X				X			X		
Imaging																		
ECG	D	7.2.2.5.7.	X	X					X				X			X	X	
Chest X-ray	D	7.2.2.5.8.		As clinically indicated														

[redacted]

Week	Category	Protocol Section	Screening Phase	Treatment Phase												Follow up Phase	
				Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9		Week 11	Week 13 Day 1 and every 4 weeks until Week 105 Day 1	End of treatment (EOT) – if before extension phase	Follow Up/Study Completion
Study Day			**-21 to -1**	**1**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**Date of last dose**	**30 days post-dose**
Abdominal MRI/CT: Phase Ib- Only patients enrolled to the confirmatory MTD level(s). Phase II- ALL patients	D	7.2.1.2.		X												X (and at week 25, week 49, and week 105)	X	
Bone Marrow biopsy and aspirate	D	7.2.1.3.		X												X (at Week 25, Week 49, Week 73, and Week 97)	X	
Safety																		
Adverse events		Perform at each visit through 30 days post last dose of study treatment																
Biomarkers																		
Whole blood sample for JAK2V617F mutational status and allelic burden analysis	D	7.2.4.1.	X													X (and at Week 25, Week 49, Week 73, and Week 97)	X (only if before the Week 97 visit)	
Whole blood sample for plasma cytokine assays	D	7.2.4.2.	X						X				X			X (and at Week 25,Week 49, and Week 105)	X	
Whole blood sample for Hh pathway analysis	D	7.2.4.3.	X				X						X			X (at Week 17, Week 25, Week 49, and Week 105)	X	
[redacted]																		
Patient reported Outcomes																		
EORTC QLQ-C30	D	7.2.6.1.2.		X					X				X			X	X	
Modified MFSAF v 2.0 questionnaire	D	7.2.6.1.1.	X	X					X				X			X	X	
LDE225 and INC424 administration	D	6.1.1.		Continuous daily dosing														

[redacted]

Week	Category	Protocol Section	Screening Phase	Treatment Phase													Follow up Phase	
				Week 1		Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9		Week 11	Week 13 Day 1 and every 4 weeks until Week 105 Day 1	End of treatment (EOT) – if before extension phase	Follow Up/Study Completion
Study Day			**-21 to -1**	**1**	**2**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**2**	**1**	**1**	**Date of last dose**	**30 days post-dose**
PK																		
Meal Record (Phase Ib and Phase II, stage 1 only)	D	7.2.3.		X									X					
PK sample (Phase Ib and Phase II, stage 1 only)	D	7.2.3.		X	X		X		X		X		X	X		X (up to Week 49)		
PK sample (Phase II stage 2 only)	D	7.2.3.		X			X		X		X		X			X (up to Week 49)		
PK sample from bone marrow aspirate (Phase II, Stage 1 or Stage 2) from at least 10 patients)	D	7.2.3.	Refer to Bone Marrow biopsy and aspirate (up to Week 49)														X	
[redacted]																		
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5.															X	X
Disposition assessment	D	7.1.3.	X														X	

[redacted]

Table 7-2 Visit evaluation schedule for Extension Phase (after Week 105 Day 1)

	Category	Protocol Section	Treatment Phase			Follow up Phase	
Week			**Every 12 weeks from Week 105**	**Every 24 weeks from Week 105**	**Every 48 weeks from Week 105**	**End of Extension Treatment (EOT)**	**Follow Up/Study Completion**
Study Day			**1**	**1**	**1**	**Date of last dose**	**30 days post-dose**
Adverse events	D		Continuously captured until Follow Up/Study Completion				
Concomitant medications/significant non-drug therapies	D	6.1	Continuously captured until Follow Up/Study Completion				
[redacted]							
Chest X-ray	D	7.2.2.5.8	As clinically indicated				
Abbreviated Physical Exam	S	7.2.2.1	As per SOC				
ECOG Performance status	D	7.2.2.4	As per SOC				
Vital signs including weight	D	7.2.2.2	As per SOC				
Urinalysis	D	7.2.2.5.5	As per SOC				
Measurement of spleen by Palpation	D	7.2.1.1	X			X	
Hematology/Chemistry	D	7.2.2.5.1 and 7.2.2.5.2	X			X	
CK	D	7.2.2.5.3	X			X	
Coagulation (INR and PTT)	D	7.2.2.5.4	X			X	
Pregnancy Urine test (women of childbearing potential only)	D	7.2.2.5.6	X				
Monthly at Home Pregnancy Testing (women of childbearing potential only)	S	7.2.2.5.6	Continuous testing during months with no visits				

[redacted]

	Category	Protocol Section	Treatment Phase			Follow up Phase	
Week			**Every 12 weeks from Week 105**	**Every 24 weeks from Week 105**	**Every 48 weeks from Week 105**	**End of Extension Treatment (EOT)**	**Follow Up/Study Completion**
Study Day			**1**	**1**	**1**	**Date of last dose**	**30 days post-dose**
Pregnancy Serum test (women of childbearing potential only)	D	7.2.2.5.6				X	
Modified MFSAF v2.0 questionnaire	D	7.2.6.1.1	X			X	
EORTC QLQ-C30	D	7.2.6.1.2				X	
ECG	D	7.2.2.5.7	As per SOC				
Dispense LDE225 and INC424		6.1	X				
LDE225 and INC424 administration	D	6.1.1	Continuous daily dosing				
Antineoplastic therapies since discontinuation of study treatment	D	7.1.5				X	X
Disposition assessment in EOT/Follow up phase	D	7.1.3				X	
Phase Ib- Only patients enrolled to the confirmatory RP2D level (expansion cohort). Phase II- ALL patients							
Abdominal MRI/CT	D	7.2.1.2		X		X	
Bone Marrow biopsy and aspirate	D	7.2.1.3			X	X	

[redacted]

7.1.1 Screening

Written informed consent must be obtained before any study specific assessments are performed, including screening.

Screening assessments must be performed within ≤ 21 days prior to receiving the first study treatment, with the exception of the serum pregnancy test, which must be performed ≤ 7 days prior to receiving the first study treatment.

Laboratory assessments that are performed as standard of care prior to consent can be used for this trial upon consenting to enter the trial if performed within ≤ 21 days prior to receiving the first study treatment.

Laboratory assessments performed as part of the screening evaluations and within 72 hours of the first dose of study treatment, are not required to be repeated on the first dosing day.

For laboratory evaluations used to determine eligibility, a repeated evaluation within the screening window is permitted for screening results out of the defined range. If the repeated laboratory result meets the criteria, that result may be used to determine eligibility. If the repeated laboratory result does not meet the criteria, the patient will be considered a screening failure.

Patient eligibility will be confirmed by the investigative staff and captured within the source documents maintained at the site. This information will be made available during planned interim monitoring visits and compared against the clinical database for accuracy. In addition, the patient eligibility eCRF should be completed, automated queries will be generated for immediate resolution should patient eligibility be in question based on the patient information entered.

Please refer to and comply with the detailed guidelines provided in the Cohort Allocation Process document and Allocation Request form.

For details on screening assessments, refer to Table 7-1.

7.1.1.1 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 screen failure.

The following eCRFs must be completed for a screen failure patient:

- Screening phase disposition page of eCRF (including reason for not being started on treatment)
- Informed Consent, including additional biomarker ICF if relevant.
- Inclusion/Exclusion Criteria
- Demography
- Adverse Events (only if the patient experienced a Serious Adverse Event during the screening period after signing the ICF (see Section 8 for SAE reporting details)

[redacted]

If a screen failure patient experiences an AE which does not meet the SAE criteria, detailsabout the AE will be recorded only in the investigator's source documents. In case of an SAE, data must be recorded on both the AE and SAE forms.

No other data will be entered into the clinical database for patients who are screen failures.

7.1.1.2 Patient demographics and other baseline characteristics

The following patient demographics and baseline characteristics will be collected on the eCRF:

- Demography including date of birth, race and ethnicity
- Height, weight (See Section 7.2.2.3)
- Diagnosis of Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential thrombocythemia Myelofibrosis
- Myelofibrosis history and prior/concomitant myelofibrosis treatment
- Cytogenetics
- Complete Medical History and current medical conditions
- Prior Myeloproliferative neoplasm directed therapy-medications
- Prior Anti-neoplastic Radiotherapy
- Prior Anti-neoplastic Surgery
- Transfusion history for the last 12 weeks prior to screening
- All other medications and non-drug therapies (including physical therapy and oxygen) administered to the patient within 30 days prior to the first dose of study drug) must be reported on the Concomitant Medications or the Surgical and Medical Procedures eCRFs
- Patient self-rating quality of life questionnaire (EORTC QLQ C-30) (See Section 7.2.6.1.2)
- Biomarker assessments (See Section 7.2.4)

Furthermore the following assessments will be performed to assess the eligibility of the patient:

- Inclusion/Exclusion (see Section 5.2 and Section 5.3)
- Physical Examination (See Section 7.2.2.1)
- Vital signs (See Section 7.2.2.2)
- ECOG performance status (See Section 7.2.2.4)
- Measurement of spleen by palpation (See Section 7.2.1.1)
- Prognostic factors for MF
- Myelofibrosis Symptom Assessment Form
- Bone Marrow Biopsy and aspirate (see Section 7.2.1.3)
- ECG (See Section 7.2.2.5.7)
- Laboratory evaluations (See Section 7.2.2.5)
- Serum pregnancy test (See Section 7.2.2.5.6)

7.1.2 Treatment period

Patients will be treated with LDE225 and INC424 for at least 2 years after the first dose or until death, documented disease progression, initiation of a new MF therapy, intolerable toxicity, withdrawal of consent, discontinuation at the discretion of the investigator, or lost to follow-up, whichever comes first. Patients who complete 2 years of treatment and are deriving clinical benefit in the opinion of the investigator will be allowed to continue receiving treatment (LDE225 and INC424) in an extension phase of this study, until discontinuation reasons are met or an alternative setting to receive study treatment (e.g., in form of another protocol) becomes available.

For details of assessments, refer to Table 7-1 and Table 7-2.

7.1.3 Discontinuation of Study Treatment

Patients may voluntarily discontinue from 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 eCRF pages. Patients 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 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 the following adverse events:
  - Grade 3 or 4 hemorrhagic event of any kind
  - Grade 3 renal toxicity for ≥ 7 consecutive days
  - Grade 4 renal toxicity
  - Grade 4 non-hematologic toxicity
  - Second occurrence of QTcF > 500 ms (≥ Grade 3) or > 60 ms change from baseline on at least two separate ECGs
  - Patient requires or undergoes splenic irradiation
  - Patient requires or undergoes splenectomy
- Any of the following laboratory abnormalities:
  - Grade 4 anemia for ≥ 7 consecutive days despite PRBC transfusions
  - Febrile neutropenia (Grade ≥ 3) (ANC < 1.0 x 109/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)
  - Grade 3 or 4 serum creatinine
  - Bilirubin > 10.0 x ULN
  - Grade 3 or 4 asymptomatic or symptomatic CK elevation with renal function impairment in which CK and creatinine levels do not return to baseline after interrupting treatment
- Pregnancy

[redacted]

- The following deviations from the prescribed dose regimen for LDE225 and INC424:
  - Interruption of study treatment for > 21 days, regardless of reason, from the intended day of the next scheduled dose. However, if the patient is obtaining clinical benefit in terms of response, the patient may continue treatment at the same or at a reduced dose following discussion between the investigator and Novartis.
  - If after 2 dose reductions and after the treatment has resumed at the lower dose, the same toxicity recurs with the same or worse severity (except for thrombocytopenia, anemia, and neutropenia)
  - If a patient cannot tolerate dose level (-1), which is the lowest acceptable dosing level for this study, except for patients in Cohort 1 who experience thrombocytopenic DLTs and can receive INC424 5mg BID and LDE225 200mg QD.
- Disease Progression
- Use of prohibited treatments (refer to Appendix 1) as determined by Novartis
- Use of another myeloproliferative neoplasm directed therapy
- Any other protocol deviation that results in a significant risk to the patient's safety
- Study is terminated by the Sponsor

Patients who discontinue study treatment should NOT be considered withdrawn from the study. They should return for the assessments indicated in Table 7-1 and Table 7-2. 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 7.1.5.

7.1.3.1 Replacement policy

Phase Ib

Dose escalation:

Patients will not be replaced on study. However, enrollment of new patients to a cohort will be considered if there is less than the minimum number of evaluable patients for the DDS.

If a patient is not treated with at least 75% of the planned doses of LDE225 and INC424 in 6 weeks (42 days) (i.e. more than 10 missed doses of LDE225 and more than 20 missed doses of INC424 in 6 weeks), the patient can continue in the study without being evaluable for DDS. Consequently, another patient has to be enrolled into the same dose level in order to reach the required number of patients in the cohort.

Enrollment of new subjects may be considered until at least the minimum number (3) or at most the maximum number (6) of evaluable subjects is achieved within a cohort, see Section 4.1.1.

Dose expansion:

No replacements will be needed, see Section 4.1.1.

[redacted]

Phase II

During Stage 1 and Stage 2 of the Phase II part of the study no replacements will be made.

7.1.4 Withdrawal of Consent

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

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

If a patient withdraws consent, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for this decision and record this information.

Study treatment must be discontinued and no further assessments conducted.

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

7.1.5 Follow-up for Safety Evaluations

All patients, including those who discontinue study treatment and those who refuse to return for an EOT visit, will be contacted for safety evaluations 30 days after the last dose of study treatment. Patients must be followed for the occurrence of Adverse Events, Serious Adverse Events, concomitant medications, antineoplastic therapies used for treating Myelofibrosis disease since discontinuation of study drug, and transfusion use. Patients whose treatment is interrupted or permanently discontinued due to an adverse event, including abnormal laboratory value, must be followed until resolution or stabilization of the event, whichever comes first. See Table 7-1 and Table 7-2 for a complete list of assessments for the 30 day follow up evaluation.

The safety follow-up may be waived if the patient is continuing INC424 and LDE treatment in an alternative setting.

Data collected should be added to the Adverse Events eCRF and the Concomitant Medications eCRF.

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 the patient, family, or family physician as agreed in the informed consent and by documenting in the source documents the 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 eCRF.

7.2 Assessment types

7.2.1 Efficacy assessments

7.2.1.1 Measurement of spleen length by manual palpation

The response assessment in the Phase Ib part of the study will consist of measuring the spleen length by manual palpation at the end of Week 24 compared to the Week 1 Day 1 measurement. Patients who have a ≥ 50% reduction in spleen size by palpation at the end of Week 24 compared to the measurement at Week 1 Day 1 will be considered responders, otherwise they will be considered non-responders. Spleen length measurements will be taken at Screening, Week 1 Day 1, every 2 weeks until Week 9 Day 1, and every 4 weeks until Week 105 Day 1. Patients in the extension phase will undergo spleen length measurements every 12 weeks from Week 105. All patients will undergo spleen length measurements at the End of Treatment visit.

The edge of the spleen shall be determined by palpation from the left costal margin to the point of greatest splenic protrusion. Palpable spleen length should be measured in centimeters and not in finger breadths.

7.2.1.2 Measurement of spleen volume by MRI/CT

Patients enrolled to the confirmatory MTD level(s) in the Phase Ib part and all patients enrolled in the Phase II part of the study will have MRI/CT of the abdomen performed at Week 1 Day 1, Week 13 Day 1, the end of Week 24, the end of Week 48, and at Week 105 Day 1. Patients in the extension phase will undergo MRI/CT of the abdomen every 24 weeks from Week 105. All patients will undergo MRI/CT of the abdomen at the End of Treatment visit. Patients who have a ≥ 35% spleen volume reduction at the end of Week 24 and Week 48 compared to Week 1 Day 1 will be considered responders, otherwise they will be considered non-responders. See Table 7-3 for the imaging collection plan.

Table 7-3 Spleen volumetric imaging (MRI/CT) collection plan

Procedure	Collection time points
Abdominal MRI of the spleen (or CT if MRI not permitted) Phase Ib- Patients enrolled to the confirmatory MTD level(s) Phase II- All Patients	Week 1 Day 1
	Week 13 Day 1
	At the end of Week 24 and the end of Week 48, and Week 105 Day 1
	Every 24 weeks from Week 105 for patients in the extension phase
	End of Treatment
Central Reader: MRI/CT scans will be sent to a central lab for analysis	

MRIs will be performed locally according to the guidelines provided by the designated imaging vendor. The scans from an individual patient will be sent to the designated imaging vendor, who will then provide an independent quantitative assessment of the spleen volume for the study. Spleen volume will be obtained by outlining the circumference of the organ and determining the volume using a validated technique. The MRI will not determine spleen length below the left costal margin, as there are no validated approaches for determining this

[redacted]

measurement. Specific image acquisition parameters and procedures will be provided by the designated imaging vendor.

MRI is the preferred method for obtaining spleen volume data. However, CT scans may be performed if MRI cannot be performed (because of the presence of metal clips in the body, or because of claustrophobia, for example), or if MRI is unavailable to the study site. CT scans will be similarly processed by the designated imaging vendor.

NOTE: Generally, the same method (MRI or CT) should be used for all visits for a given subject unless a new contraindication to the use of MRI (e.g., pacemaker insertion) occurs. Please contact the sponsor if a modality change is required.

7.2.1.3 Change in bone marrow histomorphology

Bone marrow fibrosis will be measured in grades (see Table 7-4) on biopsy samples obtained for all patients at Week 1 Day 1, Week 25 Day 1, Week 49 Day 1, Week 73 Day 1, and Week 97 Day 1. For patients in the extension phase, biopsy samples will be obtained every 48 weeks from Week 105. Biopsy samples will also be obtained at the End of Treatment visit, if a sample has not already been obtained in the past 24 weeks (see Table 7-5). Collection, processing and staining of bone marrow aspirations and biopsy samples will be done in accordance with standard procedures at the investigative sites. The bone marrow biopsy and aspirate should be assessed by an experienced hematopathologist using his/her standard examination. Bone marrow fibrosis should be graded using the European consensus grading system (Tefferi 2006).

Table 7-4 Fibrosis grading

Fibrosis Grade	Description
0	Scattered linear reticulin with no intersections corresponding to normal bone marrow
1	Loose network of reticulin with many intersections, especially in perivascular areas
2	Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis
3	Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis
Note: Fibrosis density should be assessed in hematopoietic areas.	

The following analyses should be performed:

- Assessment of cellularity.
- 500-cell differential of aspirate, correlated, if possible, with data from appropriate marrow biopsy section. Percentage of pronormoblasts, blasts, normoblasts, myelocytes, metamyelocytes
- Blast percentage, indicating what cellular types are being considered as blast equivalents, and the degree of maturation and dysplastic abnormalities within the neoplastic population should be described.
- Characterization of erythrocyte and megakaryocyte morphology.
- Characterization and gradation of fibrosis within hematopoietic cellular areas.
- Diagnostic interpretation with specific mention of (expected) absence of an infiltrative or granulomatous process

[redacted]

Cytogenetic analysis should include karyotyping and any other tests for which an abnormality has been previously identified in that subject. Any other tests that are considered standard by the Investigator may also be performed.

If samples allow, 3 unstained slides of bone marrow aspirate and half of the bone marrow biopsy sample will be sent to a central lab for central analysis. During or following the study conduct, at the Sponsor's discretion, a central review of any or all of the bone marrow studies may be conducted by external expert(s) in hematopathology.

Table 7-5 Bone marrow collection plan

Procedure	Collection time points
Bone Marrow biopsy and aspirate for local analysis (Mandatory for all patients)	Week 1 Day 1
	Week 25 Day 1, Week 49 Day 1, Week 73 Day 1, and Week 97 Day 1
	Every 48 weeks in the extension phase from Week 105
	End of Treatment (if not performed in the past 24 weeks)
* If a patient is considered to be a non-responder at the end of Week 24 then further bone marrow aspirates and/or biopsies may not be collected To central lab: if samples allow, send 3 unstained slides of bone marrow aspirate and half of bone marrow biopsy sample.	

7.2.2 Safety and tolerability assessments

Safety will be monitored by assessing adverse events, serious adverse events, laboratory evaluations (including creatine kinase), physical examinations, weight, vital signs, ECOG performance status, ECG, and chest x-rays. For details on AE collection and reporting, refer to Section 8.

7.2.2.1 Physical examination

A complete physical examination will be performed at screening and at the EOT visit. The complete physical examination comprises of a total body examination that should include: general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph-nodes, extremities, vascular and neurological review. If indicated, rectal, external genitalia, breast and pelvis exams will be performed. Subsequently, an abbreviated physical examination will be performed at Week 5 Day 1 and then monthly until Week 105 Day 1 and includes an examination of general appearance, skin, lungs, heart, and abdomen. Additional examinations may be performed at the Investigator's discretion. Patients in the extension phase will undergo abbreviated physical examinations after Week 105 per standard of care as noted in Table 7-2.

Information about the physical examination must be present in the source documentation at the study site.

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.

[redacted]

7.2.2.2 Vital signs

Vital signs (blood pressure, pulse and body temperature) will be collected according to the Visit Schedule outlined in Table 7-1 and Table 7-2 for patients in the extension phase or more frequently as per standard of care. Vital signs will be taken with the patient in the sitting position after 5 minutes of rest. Body temperature may be measured orally or via ear.

7.2.2.3 Height and weight

Height in centimeters (cm) will be measured only at screening. Body weight will be measured in indoor clothing (without shoes) at the timepoints defined in Table 7-1 and Table 7-2 for patients in the extension phase or more frequently as per standard of care.

7.2.2.4 ECOG performance status

The performance status will be assessed according to the ECOG (WHO) performance status scale (Oken 1982) at the timepoints defined in Table 7-1 and Table 7-2 for patients in the extension phase or more frequently as per standard of care. The ECOG performance status is graded on a six point scale (range 0 to 5) (See Appendix 2).

7.2.2.5 Laboratory evaluations

All safety laboratory assessments will be performed locally, at the Investigator's site laboratory according to the schedule of assessments and collection plan outlined respectively in Table 7-1 and Table 7-2 The following visit windows are allowed: +/- 1 day during the first 8 weeks (except at Week 1 Day 1 and Week 1 Day 2), +/- 2 days during Weeks 9-13 and +/- 3 days from Week 17 onwards. Laboratory-only visits can be performed at the clinic site or at any local laboratory provided that the investigator reviews the results within 2 business days to ensure subject's safety.

Novartis must be provided with a copy of the local laboratory's certification and a tabulation of the normal ranges and units of each parameter collected in the eCRF. Any changes regarding normal ranges and units for laboratory values assessed during the study must be reported via an updated tabulation indicating the date of revalidation. Additionally, if at any time a patient has laboratory parameters obtained from a different laboratory, Novartis must be provided with a copy of the certification and a tabulation of the normal ranges and units for this laboratory as well. The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance.

Non-safety laboratory samples (PK, biomarkers, biopsies) will be handled, stored and analyzed by a Novartis assigned laboratories or contracted central laboratories. Details of the collection and shipment of samples will be provided to the investigators in the laboratory manual.

At any time during the study, abnormal laboratory parameters which are clinically significant and require an action to be taken with study treatment (*e.g.*, require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for

[redacted]

Adverse events (CTCAE) version 4.0.3. Additional laboratory evaluations are left to the discretion of the investigator.

Table 7-6 Local clinical laboratory parameters collection plan

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, MCH, MCHC, MCV, Platelets, Red blood cell count (RBC), White blood cell count (WBC), RBC Morphology with Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, and Blasts)
Chemistry	Albumin, Alkaline phosphatase, ALT (SGPT), AST (SGOT), Sodium, Potassium, Calcium, Chloride, Phosphate, Magnesium, Creatinine, Glucose, Direct Bilirubin, Indirect Bilirubin, Total Bilirubin, Total Cholesterol, LDL, HDL, Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid
Muscle Toxicity Markers	Creatine kinase
Urinalysis	Microscopic Panel (Red Blood Cells, White Blood Cells, Casts, Crystals, Bacteria, Epithelial cells) Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	International normalized ratio [INR], Partial thromboplastin time (PTT)
Additional test	Pregnancy test

7.2.2.5.1 Hematology

Hematocrit, hemoglobin, MCH, MCHC, MCV, platelets, red blood cell count (RBC), white blood cell count (WBC), RBC Morphology with Differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils, and blasts) will be measured locally for Phase 1b and Phase II patients at different timepoints according to Table 7-1 and Table 7-2 for patients in the extension phase or more frequently as per standard of care.

7.2.2.5.2 Clinical chemistry

Albumin, alkaline phosphatase, ALT (SGPT), AST (SGOT), sodium, potassium, calcium, chloride, phosphate, magnesium, creatinine, glucose, direct bilirubin, indirect bilirubin, total bilirubin, total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), total protein, triglycerides, blood urea nitrogen (BUN) or urea, and uric acid will be measured locally for Phase 1b and Phase II patients at different timepoints according to Table 7-1 and Table 7-2 for patients in the extension phase or more frequently as per standard of care.

7.2.2.5.3 Muscle toxicity markers

CK will be performed according to Table 6-5 (if applicable), Table 7-1, and Table 7-2 for patients in the extension phase or more frequently to follow up on significant toxicities.

7.2.2.5.4 Coagulation

International Normalized Ratio (INR) and Partial Thromboplastin Time (PTT) will be performed locally according to Table 7-1 and Table 7-2 for patients in the extension phase or more frequently to follow up as per standard of care. In case of a hemorrhagic event of any grade (CTCAE grade 1 included) the Investigator is advised to perform unscheduled coagulation tests.

[redacted]

7.2.2.5.5 Urinalysis

Dipstick evaluations for color, bilirubin, blood, glucose, ketones, leukocytes esterase, nitrite, pH, protein, specific gravity and urobilinogen will be performed according to the visit schedule in Table 7-1 and Table 7-2 for patients in the extension phase at the local institution. If clinically indicated, any significant findings will be followed up with a microscopic evaluation to assess red blood cells, white blood cells, casts, crystals, bacteria, and epithelial cells.

7.2.2.5.6 Pregnancy and assessments of fertility

Female patients of childbearing potential must undergo a local serum pregnancy test at screening to confirm eligibility in the trial (≤ 7 days before first dose of either study drug), and at EOT as well as a urine pregnancy test locally according to the schedule of assessments outlined in Table 7-1 and Table 7-2 for patients in the extension phase.

For patients in the extension phase, monthly (or more frequently if required per local regulation) pregnancy testing is required. Women of child bearing potential will be provided with home pregnancy test kits for the duration of the study. Patients must be instructed to call the site staff for further instruction immediately if at least one of the home pregnancy tests is positive.

If an additional pregnancy test is indicated during the trial, a serum test should be performed. In case of pregnancy, the patient must permanently stop study treatment immediately, withdraw from the trial, and the pregnancy must be reported on the Clinical Trial Pregnancy Form.

7.2.2.5.7 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed locally at Screening, Week 1 Day 1, every 4 weeks until Week 105 Day 1, and at the End of Treatment (EOT) visit if before Week 105, as per Table 7-1. Patients in the extension phase (after Week 105 Day 1) will have 12 lead ECGs performed per standard of care as per Table 7-2. ECGs should be taken pre-dose while on study treatment.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. 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. Significant findings may be discussed with Novartis. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

7.2.2.5.8 Chest X-ray

If at any time during the study there is suspicion of any lung disease a chest x-ray should be performed for any patient including those in the extension phase of the study and the results recorded on the Chest X-ray eCRF and AE eCRF if applicable.

[redacted]

7.2.3 Pharmacokinetics

Blood collection

The blood sampling schedule for determining the PK of LDE225 and INC424 are provided in Table 7-7 (for Phase Ib and Phase II, Stage 1) and Table 7-9 (for Phase II, Stage 2). Blood samples for PK determinations will not be obtained during the extension phase of the study. The 24 hours plasma concentration-time profiles of LDE225 and INC424 will be characterized after single dose (Week 1 Day 1) and after multiple doses (Week 9 Day 1) in Phase Ib and Phase II Stage 1. Trough (pre-dose) samples will be collected on Week 3 Day 1, Week 5 Day 1, Week 7 Day 1, Week 9 Day 1 and Day 1 of every 4 weeks thereafter until Week 49. Only trough samples will be collected in Phase II, Stage 2. On the day of trough samples, the doses of LDE225 and INC424 should be taken at the clinic after pre-dose collection. At each scheduled time point, a single blood draw (4mL) will be collected into tubes containing K2EDTA, and the plasma will be split into 2 tubes (approximately 1 mL for LDE225 and approximately 1 mL for INC424concentration measurement). Complete instructions for sample processing, handling and shipment will be provided in the [Laboratory Manual].

If a patient experiences an adverse event that results in an unscheduled visit or fits the criteria of an SAE as determined by the Investigator, a blood sample should be collected for measurement of plasma drug concentrations.

Exact dates and clock times of drug administration and actual PK blood draw will be recorded on the appropriate eCRF. If vomiting occurs within 4 hours of dosing during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The time of vomiting should be recorded on the appropriate eCRF.

Meal records will be collected on Week 1 Day 1 and Week 9 Day 1 for Phase Ib and Phase II Stage 1 only. The start and end time of meals will be recorded.

Table 7-7 Pharmacokinetic blood collection log: Phase Ib and Phase II, Stage 1

	LDE225			INC424		
Week/Day	Time (hours)	Dose reference ID	Sample No.	Time (hours)	Dose reference ID	Sample No.
Week 1 day 1	Pre-dose	101	101	Pre-dose	201	201
	0.5	101	102	0.5	201	202
	1	101	103	1	201	203
	1.5	101	104	1.5	201	204
	2	101	105	2	201	205
	4	101	106	4	201	206
	6	101	107	6	201	207
	8	101	108	8	201	208
Week 1 day 2	Pre-dose	101*/102**	109	Pre-dose	201*/202**	209
Week 3 day 1	Pre-dose	103	110	Pre-dose	203	210
Week 5 day 1	Pre-dose	104	111	Pre-dose	204	211
Week 7 day 1	Pre-dose	105	112	Pre-dose	205	212
Week 9 day 1	Pre-dose	106	113	Pre-dose	206	213

[redacted]

Week/Day	LDE225			INC424		
	Time (hours)	Dose reference ID	Sample No.	Time (hours)	Dose reference ID	Sample No.
	0.5	106	114	0.5	206	214
	1	106	115	1	206	215
	1.5	106	116	1.5	206	216
	2	106	117	2	206	217
	4	106	118	4	206	218
	6	106	119	6	206	219
	8	106	120	8	206	220
Week 9 day 2	Pre-dose	106*/107**	121	Pre-dose	206*/207**	221
Week 13 day 1	Pre-dose	108	122	Pre-dose	208	222
Week 17 day 1	Pre-dose	109	123	Pre-dose	209	223
Week 21 day 1	Pre-dose	110	124	Pre-dose	210	224
Week 25 day 1	Pre-dose	111	125	Pre-dose	211	225
Week 29 day 1	Pre-dose	112	126	Pre-dose	212	226
Week 33 day 1	Pre-dose	113	127	Pre-dose	213	227
Week 37 day 1	Pre-dose	114	128	Pre-dose	214	228
Week 41 day 1	Pre-dose	115	129	Pre-dose	215	229
Week 45 day 1	Pre-dose	116	130	Pre-dose	216	230
Week 49 day 1	Pre-dose	117	131	Pre-dose	217	231
NA	unscheduled	NA	1001+	unscheduled	NA	2001+

Note: Pre-dose samples are taken immediately prior to LDE225 or INC424 morning dose administration.
*The former dose reference ID refers to the last dose prior to collection of the corresponding PK sample (i.e., the dose taken on the day before the trough PK sampling).
**The latter dose reference ID refers to the dose taken on the day of the PK sampling.

In Phase II Stage 1 or Stage 2, a minimum of 0.5 mL, if available, of fresh bone marrow aspirate (prior to formalin fixation) will be obtained from at least 10 patients enrolled globally at Week 25, Week 49 and EOT and will be transferred to a 1.8 mL NUNC 2D coded cryovial and centrifuged for 10 minutes at 2000 g at 3-5 degrees Celsius or room temperature. A minimum of 200 microliters of supernatant) will be transferred to a new 1.8 mL NUNC 2D coded cryovial and be frozen immediately over dry ice or in a freezer at -70 degrees Celsius. The bone marrow samples will be used for exploratory measurement of LDE225 concentrations in bone marrow (Table 7-8). A blood sample should be also collected at the time of bone marrow aspirate collection, for concurrent measurement of plasma LDE225 concentrations according to the instructions for unscheduled blood PK in the [Laboratory Manual] to understand relative distribution of LDE225 to bone marrow versus plasma.

The exact dates and clock times of bone marrow aspirate and corresponding blood PK sampling must be recorded on the respective PK blood collection CRF.

[redacted]

[redacted]

Table 7-9 Pharmacokinetic blood collection log: Phase II, Stage 2

	LDE225			INC424		
Week/Day	**Time (hours)**	**Dose reference ID**	**Sample No.**	**Time (hours)**	**Dose reference ID**	**Sample No.**
Week 1 day 1	Pre-dose	301	301	Pre-dose	401	401
Week 3 day 1	Pre-dose	302	302	Pre-dose	402	402
Week 5 day 1	Pre-dose	303	303	Pre-dose	403	403
Week 7 day 1	Pre-dose	304	304	Pre-dose	404	404
Week 9 day 1	Pre-dose	305	305	Pre-dose	405	405
Week 13 day 1	Pre-dose	306	306	Pre-dose	406	406
Week 17 day 1	Pre-dose	307	307	Pre-dose	407	407
Week 21 day 1	Pre-dose	308	308	Pre-dose	408	408
Week 25 day 1	Pre-dose	309	309	Pre-dose	409	409
Week 29 day 1	Pre-dose	310	310	Pre-dose	410	410
Week 33 day 1	Pre-dose	311	311	Pre-dose	411	411
Week 37 day 1	Pre-dose	312	312	Pre-dose	412	412
Week 41 day 1	Pre-dose	313	313	Pre-dose	413	413
Week 45 day 1	Pre-dose	314	314	Pre-dose	414	414
Week 49 day 1	Pre-dose	315	315	Pre-dose	415	415
NA	unscheduled	NA	3001+	unscheduled	NA	4001+
Note: Pre-dose samples are taken immediately prior to LDE225 or INC424 morning dose administration.						

7.2.3.1 PK analytical method

Plasma LDE225 concentrations and plasma INC424 concentrations will be measured at Novartis or a designated CRO using a validated liquid chromatography-tandem mass

[redacted]

spectrometry (LC-MS/MS) method for each analyte. Bone marrow LDE225 concentrations will be measured at Novartis or a designated CRO using a liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (e.g., exploratory or validated).

7.2.4 Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biological, pathogenic and/or pharmacologic responses to a therapeutic intervention. Investigating the Hedgehog (Hh) and JAK signaling pathways in participants enrolled in this study may illuminate any potential predictive measures of response and/or resistance to LDE225 in combination with INC424 in myelofibrosis.

[redacted]

All assessments will be performed by a Novartis designated laboratory. Instructions for collection, preparation and shipment can be found in the laboratory manual.

7.2.4.1 Blood sample for JAK status and allele burden analysis

Blood for JAK2V617F mutation status and allele burden quantitation will be analyzed at a Novartis designated laboratory.

[redacted]

7.2.4.3 Blood sample for Hedgehog pathway expression analysis

A blood sample will be collected to assess the Hh pathway activation status of each participant. This assessment will be performed by a Novartis designated laboratory and may include targets such as Gli1.

[redacted]

[redacted]

Table 7-10 Biomarker sample collection plan

Sample Type	Volume	Visit	Time point
Blood Samples			
Mandatory Whole Blood sample for JAK2V617F mutational status and allelic burden analysis	6mL (per time point)	Screening	Anytime for Screening and End of Treatment Pre-dose for all other collection timepoints
		Week 13	
		Week 25, Week 49, Week 73, and Week 97	
		End of Treatment (if before Week 97 visit)	
[redacted]			
Mandatory Whole Blood sample for Hh pathway expression analysis	2 x 2.5mL (per time point)	Screening	Anytime
		Week 3 Day 1	Pre-dose
		Week 9 Day 1	Pre-dose
		Week 17 Day 1	Pre-dose
		Week 25 Day 1	Pre-dose
		Week 49 Day 1	Pre-dose
		End of Treatment or Week 105 Day 1 (whichever comes first)	Anytime
[redacted]			

Other assessments

No additional tests will be performed on patients entered into this study.

7.2.5 Resource utilization

Not applicable.

7.2.6 Patient reported outcomes (PROs)

This study will include two efficacy questionnaires; the Seven-Day Modified Myelofibrosis Symptom Assessment Form v2.0 (MFSAF) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (see Section 7.2.6.1). Instructions for each instrument will be provided in a separate document. All PRO questionnaires should be administered in the patient's local language at the beginning of the study visit prior to any interaction with the study investigator including any tests, treatments

[redacted]

or receipt of results from any tests to avoid biasing the patient's perspective. This is to avoid potentially biasing patients or their responses to study questionnaires. The questionnaires can be given in any order.

General instructions

Patients should be given sufficient space and time to complete all study questionnaires and all administered questionnaires should be reviewed for completeness. If missing responses are noted, patients should be encouraged to complete any missing responses. Attempts should be made to collect responses to all questionnaires for all patients, including from those who discontinue prior to the study evaluation completion visit; however, if patients refuse to complete questionnaires, this should be documented in study source records. Patient's refusal to complete study questionnaires are not protocol deviations.

Completed questionnaires, including both responses to the questions and any unsolicited comments written by the patient, should be reviewed and assessed by the investigator before the clinical examination for responses which may indicate potential AEs or SAEs. This review should be documented in study source records.

7.2.6.1 Efficacy PRO questionnaires

7.2.6.1.1 Seven-day modified MFSAF v2.0

The symptoms of MF will be assessed using the Seven-day modified MFSAF v2.0 paper questionnaire. The Seven-day modified MFSAF v2.0 is a 7-item PRO instrument based on the modified MFSAF v2.0 diary (Mesa 2009, Appendix 3) to be administered at specified visits (see visit schedule). The first 6 items assess MF symptom severity at its worst as recalled in the 7 days prior to the clinic visit assessment. The symptoms measured include night sweats, itching, abdominal discomfort, pain under the ribs (left side), early satiety, and bone/muscle pain. The seventh item captures MF-related inactivity in the past 7 days prior to the clinic visit assessment. All seven items ask subjects to record their answers on an 11-point numeric rating scale, or NRS, (0 = Absent, 10 = Worst Imaginable). The first 6 items of the instrument focus on MF symptoms and are summed to create a Total Symptom score.

The Seven-day modified MFSAF v2.0 will be collected at Screening, Week 1 Day 1, then every 4 weeks until Week 105 Day 1. For patients in the extension phase, the MFSAF will be collected every 12 weeks from Week 105. All patients will complete the MFSAF at the End of Treatment visit (See Table 7-11).

7.2.6.1.2 EORTC QLQ-C30

The EORTC QLQ-C30 (Appendix 4) is one of the most widely used and validated instruments to measure health-related Quality of Life (QoL) in subjects with cancer. The EORTC QLQ-C30 includes 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), global health status/QoL and 9 symptom scale/items (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). This instrument asks the subject to respond according to the past week, with the exception of the first 5 questions that represent physical functioning and capture the subject's current status. The range of scores for all of the

[redacted]

scales is from 0 to 100. For functional and global health status/QoL scales, higher scores indicate better QoL and level of functioning; for symptom scales, higher scores indicate greater level of symptoms or difficulties.

The EORTC QLQ-C30 will be collected at Week 1 Day 1, then every 4 weeks until Week 105 Day 1. For patients in the extension phase, the QLQ-C30 will be collected every 12 weeks from Week 105. All patients will complete the QLQ-C30 at the End of Treatment visit (See Table 7-11).

Table 7-11 MFSAF v2.0 and EORTC QLQ-C30 collection plan

Patient Questionnaire	Visit	Time point
MFSAF v2.0	Screening	Prior to any clinical assessments, study drug dosing, or diagnostic testing
	Week 1 Day 1, then every 4 weeks until Week 105 Day 1	
	Every 12 weeks for patients in the extension phase	
	End of Treatment	
EORTC QLQ-C30	Week 1 Day 1, then every 4 weeks until Week 105 Day 1	
	Every 12 weeks for patients in the extension phase	
	End of Treatment	

8 Safety monitoring and reporting

8.1 Adverse events

8.1.1 Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g., hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

For patients who sign the ICF, all AEs will be captured in the AE eCRF from time of signature through 30 days after permanent study drug discontinuation. For patients who fail screening, only SAEs will be captured in the AE eCRF page.

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

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the

[redacted]

severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected on the appropriate eCRF.

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

1. The severity grade (CTCAE Grade 1-4)
2. Its duration (Start and end dates)
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 taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 8.2.1.

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

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

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

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

8.1.2 Laboratory test abnormalities

8.1.2.1 Definitions and reporting

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of

[redacted]

the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

8.2 Serious adverse events

8.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - 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
- Protocol exempt SAEs: Any SAEs that are expected due to the condition being treated and where there has been a clear agreement with regulators not to collect these SAEs in the safety database, provided the information is collected elsewhere. For example, this may include serious adverse events that are also a primary outcome measure, such as mortality, survival rate or number of flares of the condition being studied.

8.2.2 Reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided main 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.

SAE collection starts at time of main ICF signature whether the patients is a screen failure or not.

[redacted]

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

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

When SAEs are recorded electronically in the RDC system, these should be entered, saved and e-signed **within 24 hours of awareness of the SAE**. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first.

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

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

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

8.3 Emergency unblinding of treatment assignment

Not applicable.

[redacted]

8.4 Pregnancies

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 up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

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

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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's Brochure. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

8.6 Data Monitoring Committee

Not applicable.

8.7 Steering Committee

A steering committee (SC) will be established for the Phase II part of the study and will be comprised of investigators participating in the study and Novartis representatives.

The SC will ensure transparent management of the study according to the protocol by recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate and key safety data at regular intervals during the study. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. Full details on the role of the SC will be defined in a SC charter.

9 Data collection and management

9.1 Data confidentiality

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

[redacted]

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

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

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

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

9.2 Site monitoring

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

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

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

9.3 Data collection

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

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

Electronic versions of the EORTC QLQ-30 and MFSAF v 2.0 questionnaires will be provided to the sites, sites will print paper copies of these questionnaires for the patients. The questionnaires must be completed by patients, scored and interpreted at each applicable visit (see Table 7-1). The total score will be determined by the investigator (or designee) and will be interpreted for each questionnaire separately. Answers provided by the patients on the questionnaires will be entered manually by the investigator site staff into the eCRF. Original questionnaires will be archived in patient medical files. The field monitor will review the relevant questionnaires and eCRFs for accuracy and completeness.

All ECGs will be read locally.

PK, biomarker (blood and derivative) and bone marrow biopsy/aspirate samples obtained during the course of the study will be collected from the investigator sites and analyzed by Novartis assigned laboratories or contracted central laboratories. The site staff designated by the investigator will enter the information required by the protocol onto the respective sample collection eCRFs, as well as onto the designated CRO's requisition form. One copy of the requisition form will be sent to the designated laboratory (including study number, subject ID, etc.) and one copy will be retained by the site. The field monitor will review the relevant eCRFs for accuracy and completeness and will work with the site staff to adjust any discrepancies as required. The field monitor will also review the requisition forms for completeness.

Imaging Data used to assess spleen volume will be centrally collected and subjected to quality control.

9.4 Database management and quality control

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

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

[redacted]

ECGs will be read locally. Samples and/or data for imaging, PK, Biomarker (blood and derivative), and bone marrow biopsies/aspirates will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

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

10 Statistical methods and data analysis

Data from this trial will be analyzed by Novartis and/or a designated CRO. All data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

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

The final analysis of study data for the purposes of generating the Clinical Study Report (CSR) will be based on all patient data from phase I (including dose escalation and safety expansion phases), phase II, and the extension phase, when all patients have discontinued the study.

Details of the statistical analysis and data reporting will be provided in the Novartis Report and Analysis Plan (RAP) document finalized before database lock.

10.1 Analysis sets

The following analysis sets will be used for statistical analysis and data reporting.

10.1.1 Full Analysis Set

Phase Ib:

The Full Analysis Set (FAS) comprises all patients in phase Ib who received at least one dose of LDE225 and/or INC424. This includes the dose escalation and safety expansion portions of the study.

Phase II:

The FAS comprises all patients in phase II who received at least one dose of LDE225 and/or INC424.

Patients will be classified according to the assigned treatment combination. Unless otherwise specified the FAS will be the default analysis set used for all analysis.

Patients who are screened but never start treatment will be listed and will not be included in any of the summary tables.

10.1.2 Safety Set

Phase Ib:

[redacted]

The Safety Set includes all patients in phase Ib who received at least one dose of LDE225 and/or INC424.

Phase II:

The Safety Set includes all patients in Phase II who received at least one dose of LDE225 and/or INC424.

Patients will be analyzed according to the study treatment (regimen) they actually received, where treatment received for each drug is defined as (i) the treatment assigned if it was received at least once, or (ii) the first treatment received when starting study medication. Each patient will be classified into and analyzed consistently within one (and only one) treatment group.

10.1.3 Dose-determining analysis set

The dose-determining set (DDS) consists of all patients from the safety set of phase Ib who either meet the following minimum exposure criterion and have sufficient safety evaluations (as determined by the investigators and Novartis), or discontinue earlier due to DLT. This constitutes an evaluable patient for the determination of the MTD.

A patient is considered to have met the minimum exposure criterion at treatment group if the patient receives at least 75% of the planned doses of LDE225 **and** INC424 within 6 weeks (42 days) following the first dose (i.e., no more than 10 missed doses of LDE225 and no more than 20 missed doses of INC424 in 6 weeks are permitted). Patients who do not meet these minimum exposure and safety evaluation requirements will be regarded as ineligible for inclusion into the DDS. Patients in the DDS will be identified before database lock

10.1.4 Pharmacokinetic analysis set

Phase Ib:

The pharmacokinetic analysis set (PAS) consists of all patients in Phase Ib who receive at least one (full or partial) dose of LDE225 and/or INC424 and provide at least one evaluable PK blood sample for LDE225 and/or INC424.

Phase II:

The PAS of phase II consists of all patients in Phase II who receive at least one (full or partial) dose of LDE225 and/or INC424 and provide at least one evaluable PK blood sample for LDE225 and/or INC424 or both).

The PAS will be used for summaries of PK data (Tables and Figures) as well as for listing of derived parameters.

10.1.5 Biomarker analysis set

The Biomarker Analysis Set (BAS) consists of all patients who receive at least one (full or partial) dose of LDE225 and/or INC424 and provide at least one evaluable biomarker sample.

[redacted]

10.2 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics and ECOG (WHO) performance status) will be summarized descriptively by study phase (phase Ib and phase II). Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

10.3 Treatments (study treatment, concomitant therapies, compliance)

10.3.1 Study treatment

The actual dose and duration in days of LDE225 and INC424 treatment as well as the dose intensity (computed as the ratio of actual received and actual duration) and the relative dose intensity (computed as the ratio of dose intensity and planned dose received/planned duration) will be listed and summarized by means of descriptive statistics by treatment group and by study phase in the clinical study report.

10.3.2 Concomitant therapies

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized for the full analysis set by study phase.

10.3.3 Compliance

Compliance with the study protocol will be assessed by reporting the number and type of protocol deviations. These will be identified prior to database lock and will be listed and summarized by study phase.

10.4 Primary objective

The primary objective of Phase Ib is to establish the MTD and/or RPIID of the combination of LDE225 (QD) and INC424 (BID) when administered orally to patients with myelofibrosis who have not previously received therapy with a JAK inhibitor.

The primary objective of Phase II is to assess the efficacy of the co-administration of LDE225 and INC424 on spleen volume reduction as determined by centrally reviewed MRI/CT.

10.4.1 Variable

Phase Ib:

The primary variable is the frequency of DLTs associated with continuous daily administration of LDE225 in combination with INC424 as a function of dose. Estimation of the MTD of the combination treatment will be based upon the estimation of the probability of DLT at each dose level using BLRM and guided by EWOC (Section 10.4.2).

Phase II:

The primary endpoint is the proportion of subjects achieving ≥ 35% reduction in spleen volume from baseline by centrally reviewed MRI/CT at the end of Week 24 and Week 48.

[redacted]

10.4.2 Statistical hypothesis, model, and method of analysis

Phase Ib:

Dose escalation

An adaptive Bayesian logistic regression model (BLRM) similar to the proposal by (Thall 2003) and dose escalation criteria proposed by (Babb 1998) will be used for the dose escalation.

A 6-parameter Bayesian Logistic Regression Model (BLRM) for combination treatment will be fitted to the 6-week dose-limiting toxicity data (i.e. absence or presence of DLT) accumulated throughout the dose escalation part to model the dose-toxicity relationship of LDE225 and INC424 when given in combination. The model is formulated in the following way: let $\pi_1(d_1)$ be the probability of a DLT if INC424 is given as a single agent as dose d_1, and let $\pi_2(d_2)$ the probability of a DLT if LDE225 is given as a single agent at dose d_2, further let $\pi_{12}(d_1,d_2)$ be the probability of a DLT when LDE225 and INC424 are given in combination at doses d_1 and d_2 respectively. The dose-DLT relationship is then modeled as:

For a single-agent INC424: $\text{logit}(\pi_1(d_1))=\log(\alpha_1)+\beta_1\log(d_1/d_1^*)+\gamma I(\text{PLT}\leq 200X10^9)$,

For a single-agent LDE225: $\text{logit}(\pi_2(d_2))=\log(\alpha_2)+\beta_2\log(d_2/d_2^*)$,

For the combination of LDE225 and INC424:

$$\text{Odds}(\pi_{12}(d_1,d_2))= \pi_{12}(d_1,d_2)/(1- \pi_{12}(d_1,d_2))$$
$$=\exp(\eta\, d_1/ d_1^*\, d_2/ d_2^*)(\pi_1(d_1)+ \pi_2(d_2)- \pi_1(d_1)\, \pi_2(d_2))/((1- \pi_1(d_1))(1- \pi_2(d_2))),$$

Where I is the indicator function, $\text{logit}(\pi(d))=\log[\pi(d)/\{1- \pi(d)\}]$, $d_1^*=30$ mg total daily dose (15 mg BID) and $d_2^*=700$ mg(QD) are the reference doses of INC424 and LDE225 respectively, α_1, α_2, β_1, β_2, η and $\gamma>0$ are model parameters. The parameter γ is related to the binary baseline covariate (platelet count at baseline $\leq 200X10^9$/L) and η is an interaction term between the two drugs.

Prior specifications: LDE225 and INC424

The priors used in this study are listed in Table 10-1.

Table 10-1 Prior specifications

Parameter	Means	Standard deviations	Correlation
INC $\log(\alpha_1),\log(\beta_1)$	(-2.141,-0.180)	0.602,0.634	0.085
LDE $\log(\alpha_2),\log(\beta_2)$	(-2.291,0.721)	0.894,0.773	-0.117
η (normal)	0.250	2.028	n/a
γ (log-normal)	-1.426	1.61	n/a

The derivation of these priors and simulated operating characteristics can be found in detail in Appendix 7 (Section 14.7).

Dose recommendation

Dose recommendation will be based on summaries of the posterior distribution of model parameters and the posterior distribution of DLT rates, including the mean, median, standard

[redacted]

deviation, 95%-credibility interval, and the probability that the true DLT rate for each dose combination lies in one of the following categories:

- [0%, 16%) under dosing
- [16%, 35%) targeted toxicity
- [35%, 100] excessive toxicity

Following the principle of EWOC, after each cohort of patients the recommended dose combination is the one with the highest posterior probability of DLT in the target interval [16%, 35%) among the doses fulfilling the overdose-control criterion that there is less than 25% (posterior probability) chance of excessive toxicity. In addition, the maximum inter-cohort dose escalation is limited to 100% (i.e. up to 100% and 0% increase for LDE225 and INC424 respectively or 0% and up to 100% increase for LDE225 and INC424 respectively). The proposed combination meets the EWOC criteria (i.e. less than 25% chance that the true rate of DLTs lies within the interval [35% - 100%]. A clinical synthesis of the available toxicity information (including AEs that are not DLTs), PK, PD, and efficacy information as well as the recommendations from the BLRM will be used to determine the dose combination for the next cohort at a dose escalation teleconference. The determination of MTD/RPIID will occur when the following conditions are met:

1. at least 9 patients have been treated at each MTD and/or RPIID dose,
2. this dose satisfies one of the following conditions:
   a. the posterior probability of targeted toxicity at this dose exceeds 50%, or
   b. minimum of 24 patients have already been treated on the trial.

Safety Expansion

After declaration of MTD and/or RPIID, the dose will be expanded by an additional 6 patients in order to further assess tolerability, safety and early efficacy. If two MTDs/RPIIDs are established, each MTD/RPIID will enroll an additional 6 patients in the safety expansion. After these confirmatory patients have been treated for 6 weeks, if 2 or more DLTs are observed at the selected dose (MTD/RPIID), the BLRM will be ran again to confirm that the current dose still satisfies the overdose criteria of the model. If the dose fails to satisfy the criteria, a change to the dose under study will be made subject to the BLRM recommendation.

Listing of DLTs

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

Phase II:

In the final analysis, the uniformly minimum variance unbiased estimator (UMVUE; Jung 2004) for the proportion of subjects achieving ≥ 35% reduction from baseline in spleen volume as measured by MRI/CT at the end of Week 24 weeks Week 48, and their exact two-sided 95% confidence intervals will be provided. Patients with unknown response will be treated as non-responders (see Section 10.4.3).

[redacted]

10.4.3 Handling of missing values/censoring/discontinuations

The reasons for discontinuation from the study will be summarized and listed, along with dates of first and last study drug taken, duration of exposure to study drug and date of discontinuation for each patient. Other missing data will simply be noted as missing on the appropriate tables/listings.

Phase Ib:

Patients in the dose escalation phase are ineligible for the dose-determining set will not be replaced. However, if adequate numbers of evaluable patients are not available per cohort then additional patients may be enrolled.

Phase II:

Patients with unknown clinical response (e.g. patients with missing assessments at the end of 24 or 48 weeks) will be considered as non-responders. No imputation of missing values will be made for the efficacy analysis.

10.4.4 Supportive analyses

Additional supportive analysis may be conducted if appropriate.

10.5 Secondary objectives

The following secondary objectives will be performed (Table 10-2).

Table 10-2 The analysis for the list of secondary objectives

Objective	Analysis
Phase Ib	
To evaluate the safety of the co-administration of LDE225 and INC424 in patients with MF	Refer to Section 10.5.
To characterize the single and multiple dose pharmacokinetics following the co-administration of LDE225 and INC424	Refer to Section 10.5.2.
Phase II	
To assess the effect of the co-administration of LDE225 and INC424 on bone marrow fibrosis by central review and on disease-specific pharmacodynamic biomarkers as a function of the molecular disease characterization of MF	Refer to Section 10.5.3.1.
To evaluate the safety of the co-administration of LDE225 and INC424 in patients with MF	Refer to Section 10.5.1.
To characterize pharmacokinetics following the co-administration of LDE225 and INC424	Refer to Section 10.5.2.
To assess the effect of the co-administration of LDE225 and INC424 on MF-associated symptoms burden	Refer to Section 10.5.4.

10.5.1 Safety

The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g., electrocardiogram, vital signs) will be considered as appropriate. The safety summary tables

[redacted]

will include only assessments collected no later than 30 days after study treatment discontinuation. All safety data will be listed.

10.5.1.1 Adverse events (AEs)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, i.e. the ***treatment-emergent*** AEs. On-treatment assessment is defined as any assessment reported in the time interval from the start date of study treatment to 30 days following the last date of study treatment. However, all safety data will be listed and data collected outside the on-treatment period will be flagged.

The incidence of treatment-emergent adverse events (new or worsening from baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE 4.03 grades), type of adverse event, relation to each treatment schedule and by study phase.

Deaths and serious adverse events will be listed by patient and tabulated by type of adverse event and each treatment schedule by study phase.

10.5.1.2 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, laboratory data will be graded accordingly. All laboratory values will be converted into SI units. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

The following by-treatment summaries will be generated separately for hematology, biochemistry and urinary laboratory tests by study phase:

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

In addition to the above mentioned tables and listings, other exploratory analyses may be performed as appropriate.

10.5.1.3 Other safety data

Summary statistics for data from other tests will be provided, notable values will be flagged, and any other information collected will be listed as appropriate by study phase. Descriptive summary statistics will be provided for electrocardiogram (ECG) and vital sign data, as follows:

- ECG: Changes from baseline to end of study, and new or worsening abnormalities.
- Vital signs: Summary statistics of raw data and change from baseline values (means, medians, standard deviations) plus newly occurring or worsening abnormalities.

Listings with flagged notable values and any other information collected will be provided as appropriate.

[redacted]

10.5.2 Pharmacokinetics

Plasma concentrations of LDE225 and INC424 will be summarized at each scheduled time point by dose level. Descriptive graphical plots of individual plasma concentrations over time will be generated, along with mean concentration time profiles and trough for LDE225 and INC424. A list of individual concentrations will be provided using FAS.

For Phase Ib and Phase II Stage 1 only, PK parameters listed in Table 10-3 and Table 10-4 will be determined for all PK-evaluable patients using non-compartmental method(s) using WinNonlin or Phoenix WinNonlin (Pharsight, Mountain View, CA). PK parameters will be estimated for Week 1 and Week 9 and reported, when feasible. PK parameters in Table 10-3 and Table 10-4 for LDE225 and INC424 will be descriptively summarized for Week 1 and Week 9 by dose level. For Phase II Stage 2, Ctrough will be descriptively summarized at each scheduled time point and by means of graphical display.

Descriptive statistics (n, mean, SD, CV%, median [range], and geometric mean and CV%) will be presented for all parameters with the exception of Tmax for which median values and ranges will be presented. When a geometric mean is presented, it will be stated as such.

[redacted]

Table 10-3 Noncompartmental pharmacokinetic parameters for LDE225 (Phase Ib and Phase II Stage 1 only)

Term	Definition
Cmax	Maximum observed plasma concentration after drug administration [mass x volume^{-1}]
Tmax	Time to reach C_{max} [time]
AUC0-24h	Area under the concentration-time curve from time zero to 24 hours [mass x time x volume^{-1}]

Table 10-4 Noncompartmental pharmacokinetic parameters for INC424 (Phase Ib and Phase II Stage 1 only)

Term	Definition
Cmax	Maximum observed plasma concentration after drug administration [mass x volume^{-1}]
Tmax	Time to reach Cmax [time]
AUClast	Area under the concentration-time curve from time zero to the time of last measurable concentration [mass x time x volume^{-1}]
AUC0-12h	Area under the concentration-time curve from time zero to 12 hours extrapolate from AUClast[mass x time x volume^{-1}]
AUCinf	Area under the concentration-time curve from time zero to infinity with extrapolation of the terminal phase [mass x time x volume^{-1}]
T1/2	Elimination half-life associated with the terminal slope (lambda_z) of a semi logarithmic concentration-time curve [time]
CL/F	Apparent total plasma clearance of drug after oral administration [volume x time^{-1}]
Racc	Accumulation ratio calculated as AUC on Week 9 Day 1 divided by AUC on Week 1 Day 1 [fold]
Vss/F	Apparent volume of distribution at steady state after oral administration [volume]

[redacted]

10.5.2.1 Data handling principles

All concentrations below the limit of quantitation or missing data will be reported as such in the concentration data listings. Concentrations below the limit of quantitation will be treated as zero in summary statistics.

10.5.3 Biomarkers

This study is not adequately powered to assess specific biomarker-related hypotheses, thus statistical analyses of these data should be considered exploratory in nature. Analytical results from such analyses may be used to generate additional hypotheses that must then be verified with data derived from subsequent clinical trials.

Summary tables, listings and visual displays will be created in order to describe the data, detect trends and draw preliminary conclusions. If sample size permits, advanced analyses may be carried out to better understand the data, refine interpretation and generate more robust hypotheses. Furthermore, additional post hoc exploratory assessments are expected and may be performed. The data analysis will be described in the biomarker analysis plan (BAP).

There may be circumstances when a decision is made to stop sample collection, or not perform or discontinue the analysis of biomarker samples due to either practical or strategic reasons (e.g. issues related to the quality and or quantity of samples, or issues related to the assay that preclude the analysis of samples). Under such circumstances, the number of samples may be inadequate to perform a rigorous data analysis and the available data will only be listed.

10.5.3.1 Outline of the data analysis

The proposed data analysis is aligned with the exploratory biomarker objective of the study protocol. The analysis of biomarker data collected at baseline will include basic descriptive statistics for all enrolled patients and by dosing schedule and/or treatment group and for the full population. If post baseline biomarker data are collected, distribution of change from baseline data will also be described. Where appropriate; baseline values and/or change from baseline values of biomarker and mutational status will be described with respect to clinical endpoints of interest. Exploratory subgroup analysis according to some of the baseline biomarker data may be performed. In addition, the association between biomarker levels or change in biomarker levels with PK, efficacy or safety endpoints may also be explored via suitable statistical analysis or graphical aids. For instance scatter plots/strip plots of biomarkers at baseline versus response may be created. Results from these exploratory analyses may be summarized in the clinical study report or in a separate document.

10.5.3.2 Data handling principles for biomarkers

Detailed data handling methods will be addressed in the RAP or in a stand-alone analysis plan document, as appropriate. These details may include (but are not limited to) descriptions of data transformations, approach to handle measures below the lower limit of quantification (LLOQ), thresholds and algorithms used to categorize and combine biomarkers etc.

10.5.3.3 Data analysis principles

10.5.3.3.1 Analysis sets

The standard analysis sets will be used instead according to the purpose of a given analysis (e.g. FAS to describe biomarkers, safety/per-protocol set to assess the relationship between biomarkers and selected safety/efficacy endpoints). Note that since no imputation is usually planned, the number of patients included in a given analysis will reflect the number of patients in the chosen analysis set which have a valid biomarker assessment.

10.5.3.3.2 Basic tables, figures and listings

Mutations involved in the molecular disease characterization of MF will be listed by patient and summarized using frequency tables by dose cohort. Association with efficacy endpoints (spleen volume reduction) and mutation status will be assessed graphically via strip plots or frequency tables of mutational status group and response categories (≥ 35% reduction and < 35% reduction in spleen volume) by dose cohorts.

The expression levels of Hh pathway related biomarkers (such as Gli1), cytokine levels and allele burden (reported as percent mutated) will be reported and summarized as follows:

All data will be listed by dosing schedule, patient and time point. Summary tables of the expression levels will be created at each measured time point by doing schedule and all dosing groups combined. Summary tables will include number of samples (n), % of those samples below LLOQ, mean, standard deviation, median, %CV, minimum and maximum. For all post-baseline time-points; fold change in biomarker expression levels will also be summarized. The summary statistics will include, number of samples, mean, geometric mean, %CV of geometric mean, minimum, maximum etc. Additionally frequency tables (number and percentage of subjects) for JAK2 mutation status (positive/negative) at baseline will be reported.

Longitudinal plots of the mean fold-change from baseline along with 95% CI's or standard error bars will be created to explore the trend over time. Additionally, a mixed model analysis of log2 (fold change from baseline) ~ log2 (baseline level) + dose schedule + time + dose schedule*time may be carried out. In that case, longitudinal plots of model adjusted means for each dose schedule over time, together with the 95% confidence intervals will be may be created to view trends over time. Strip plots or scatter plots of baseline or change from baseline in biomarker levels versus end-point of interest (spleen volume reduction) may also be produced to explore the association with efficacy.

The associations between biomarkers and efficacy outcomes may also be explored via more sophisticated statistical models if sufficient data are available.

10.5.3.3.3 Advanced analysis methods

Advanced statistical analysis may be carried out to explore the data in a post-hoc fashion.

These methods will typically be used to build a model to estimate, classify or predict the relationship between the explanatory variable(s) and the dependent variables (e.g. linear mixed models fitted on longitudinal data to quantify time-related changes or models to predict

[redacted]

response based on baseline gene expression levels) or to identify patterns and similarities in the data by establishing relationship among all variables (e.g. hierarchical clustering of patients into subgroups according to their biomarker profile). Variable selection, predictive modeling and surrogacy methodologies may be applied to explain and predict response to treatment.

Details of such methodology if applied to the data will be described in a separate Biomarker Analysis Plan document.

10.5.4 Patient Reported Outcomes (Seven-day modified MFSAF v2.0 and EORTC QLQ-C30)

The Seven-day Total Symptom Score (TSS) and individual item scores from MFSAF will be summarized descriptively along with changes from baseline to each visit where the variable is measured. At week 24 the proportion of patients who have a ≥50% reduction from baseline in total symptom score based on the Seven-day modified MFSAF v2.0 will be determined as follows.

The Seven-day TSS will be defined as the sum of 6 individual symptom scores (each scored on a 0-10 point scale) collected on the same day. The score will be missing if there are any missing individual scores and inactivity will not be included.

The percent change will be calculated by:

- % change=100x(Week 24 Total Score-Baseline Total Score)/Baseline Total Score

The percent of patients who have a ≥50% reduction in TSS at week 24 will be estimated with a two-sided 95% confidence interval. Similar summary will be presented for each of the individual symptom scores. A waterfall graph will be presented to display the percent change from baseline in Total Symptom Score for each patient at Week 24.

The EORTC QLQ-C30 subscales and individual item scores will be summarized descriptively along with changes from baseline to each visit where the variable is measured.

[redacted]

10.7 Interim analysis

There will be an interim analysis for both safety and efficacy after 18 patients are enrolled in the phase II study. After the first 18 patients are enrolled and observed over a minimum of 24 weeks or until death, documented disease progression, intolerable toxicity, withdrawal of consent, discontinuation at the discretion of the investigator or lost to follow-up, whichever comes first, further enrollment can be stopped for futility if there are less than 8 responders (i.e., spleen volumetric reduction of at least 35% through MRI/CT). This corresponds to a decision threshold of >20% (Bayesian) predictive probability of success to continue enrollment (Table 10-6).

Review of safety data will include, but is not limited to, assessment of the nature and frequency of deaths during treatment, serious adverse events, Grade 3 or 4 adverse events, key laboratory abnormalities, abnormal results from electrocardiogram (ECG) assessments and distribution of safety-related reasons for discontinuation. The trial might be terminated at the interim if treatment is not well tolerated as determined by steering committee (Grade 3-4 AEs >20% may result in termination).

It is possible to terminate the trial at the interim for lack of adequate efficacy, i.e. futility. Assessment of futility will be based on the calculated Bayesian predictive probabilities for the occurrence of the response rate in the FAS.

The efficacy outcome (response rate) is assumed to be binary, namely, response (achieving ≥ 35% reduction of spleen volume from baseline by centralized reviewed MRI/CT, Yes vs. No), and the number of responders follow a binomial distribution.

Suppose the prior belief regarding the probability of response (π) is that it has a beta distribution with parameters α_0 and β_0. If there are x responders out of n patients, then the posterior distribution for π is beta distribution with parameters $\alpha_1 = \alpha_0 + x$ and $\beta_1 = \beta_0 + n - x$. Now let Y represent the number of success from m future observations, then the posterior predictive distribution of Y conditional on the observed data at the interim (x responders out of n patients) is a betabinomial distribution described by

$$p(Y = y|x,n) = \binom{m}{y} \frac{B(\alpha_0 + x + y, \beta_0 + n - x + m - y)}{B(\alpha_0 + x, \beta_0 + n - x)}$$

Where B(a,b) is the beta distribution with parameter a and b.

The prior for the response rate is assumed to follow a Beta(1,1) distribution, which corresponds to a priori expectation of 50%. If there are 8 or more responders, after the first 18 patients have been observed for 24 weeks, then 28 additional patients will be enrolled into stage 2. Encouraging efficacy will be concluded if the observed ORR exceeds 50% (i.e. 23/46) at the end of Phase II.

In this study, futility is equivalent to observe less than 8 responders in 18 patients (Table 10-6). However, the cut-off for the number of responders needed will be determined at the time of interim analysis based on the actual number of patients enrolled in the study following the algorithm defined in the protocol.

[redacted]

Table 10-6 Predictive probability of observing response rate of 50% (n=18) or greater in the FAS at the primary analysis (46 patients) under different interim results

Observed response at IA		
# of response	%	Predictive probability of observing response rate ≥50%
4	22.2	0.002
5	27.8	0.011
6	33.3	0.047
7	38.9	0.143
8	44.4	0.318
9	50.0	0.548
10	55.6	0.762
11	61.1	0.905
12	66.7	0.972
13	72.2	0.994

10.8 Sample size calculation

The total sample-size for the study will be approximately 82.

Phase Ib: Approximately 36 patients are expected to be enrolled into dose escalation cohorts. Cohorts of 3 to 6 evaluable patients per dose level will typically be enrolled in the dose escalation part including at least 6 evaluable patients at the MTD level. Assuming a total of 5 cohorts, the number of patients during dose escalation is expected to be approximately 30. An additional 6 patients will be treated at the MTD/RPIID during the safety expansion. If two MTDs/RPIIDs are established, each MTD/RPIID will enroll additional 6 patients in the safety expansion.

Phase II: Following the determination of an MTD or RPIID in phase Ib, 18 patients will be enrolled in the first stage and if the criterion is met to continue to stage 2, an additional 28 patients will be enrolled.

Operating Characteristics

Phase Ib: The operating characteristics of the BLRM guided by EWOC used in the study is provided in Appendix 7 (Section 14.7).

Phase II: In terms of the frequentist operating characteristics, based on the sample size of 46 patients in phase II, the design has a false-positive rate (type I error) of 9.5% when the true ORR is 40% (representing no benefit) and a true-positive rate (power) of 90% when the true ORR is 60%. The operating characteristics in this study are in Table 10-7.

Table 10-7 Decision of operating characteristics for the primary endpoint of CLDE225X2216 study design

True ORR	Probability of observing an ORR ≥ 50%
0.30	0.003
0.35	0.022
0.40	0.095
0.45	0.263

[redacted]

True ORR	Probability of observing an ORR ≥ 50%
0.50	0.508
0.55	0.745
0.60	0.900
0.65	0.970
0.70	0.993
0.75	0.999

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.

11.3 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB approved informed consent. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents. The date when a subject's Informed Consent was actually obtained will be captured in the eCRF.

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

Women of child bearing potential and sexually active males should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur

[redacted]

during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

11.4 Discontinuation of the study

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

11.5 Publication of study protocol and results

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

11.6 Study documentation, record keeping and retention of documents

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

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

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site Principal Investigator. The study case report form (CRF) is the primary data collection

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

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

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

11.7 Confidentiality of study documents and patient records

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

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. United Kingdom requires the notification of urgent safety measures within 3 days) but not later than 10 working days.

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[redacted]

14 Appendices

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

14.1.1 Concomitant medications requiring caution

Table 14-1 Medications that are known substrates of BCRP to be used with caution

BCRP substrates			
Nitrofuratoin	Pantoprazole	sulfasalazine	zidovudine

Table 14-2 List of weak CYP3A inducers or inhibitors to be used with caution

Weak CYP3A inducers			
armodafinil (R-modafinil)	bexarotene	clobazam	danshen
dexamethasone	Echinacea	garlic (allium sativum)	glycyrrhizin
methylprednisolone	nevirapine	oxcarbazepine	pioglitazone
pleconaril (not available in US market)	prednisone	primidone	raltegravir
rufinamide	terbinafine	topiramate	troglitazone (not available in US market)
Weak CYP3A inhibitors			
alprazolam	amlodipine	azithromycin	bicalutamide
chlorzoxazone	cilostazol	clotrimazole	cranberry juice
cyclosporine	delavirdine	drospirenone	ethinyl estradiol
fluvoxamine	fosaprepitant	isoniazid	lacidipine
linagliptin	norgestimate	peppermint oil	pravastatin*
propiverine	ranitidine	ranolazine	resveratrol
roxithromycin (not available in US market)	seville orange juice	sitaxentan	tabimorelin
tacrolimus	tolvaptan		

*If it is essential that the patient takes a statin to control hyperlididemia, then only pravastatin may be used with extra caution.

Table 14-3 List of CYP2B6 and 2C9 substrates to be used with caution

CYP2B6 substrates			
bupropion			
CYP2C9 substrates			
celecoxib	diclofenac	flurbiprofen	glipizide
glyburide	gliclazide	glimepiride	lornoxicam
indomethacin	irbesartan	ketobemidone	nateglinide
losartan	meloxicam	naproxen	piroxicam
S-ilbuprofen	sulfamethoxazole	tenoxicam	tolbutamide
torasemide	valdecoxib		

[redacted]

Table 14-4 List of permitted antifungal and antibiotic agents to be used with caution

Permitted antifungal and antibiotic agents to be used with caution			
amphotericin B	anidulafungin	azithromycin	candicidin (not available in US market)
caspofungin	clotrimazole	flucytosine	griseofulvin
isoniazid	micafungin	nystatin	roxithromycin (not available in US market)
terbinafine			

14.1.2 Prohibited co-medications

Table 14-5 List of prohibited CYP3A inducers or inhibitors

Moderate/Strong CYP3A inhibitors			
amprenavir	aprepitant	atazanavir	boceprevir
casopitant	cimetidine	ciprofloxacin	clarithromycin
cobicistat	conivaptan	darunavir	diltiazem
dronedarone	elvitegravir	erythromycin	FK1706
fluconazole	fosamprenavir	grapefruit juice	imatinib
indinavir	itraconazole	ketoconazole	lopinavir
mibefradil	nefazodone	nelfinavir	posaconazole
ritonavir	saquinavir	schisandra sphenanthera	telaprevir
telithromycin	tipranavir	tofisopam	troleandomycin
verapamil	voriconazole		
Moderate/Strong CYP3A4 inducers			
avasimibe	bosentan	carbamazepine	efavirenz
etravirine	genistein	mitotane	modafenil
nafcillin	phenobarbital	phenytoin	rifabutin
rifampin (rifampicin)	ritonavir	St. John's wort	talviraline (not available in US market)
thioridazine	tipranavir		

Table 14-6 List of prohibited CYP2B6 and CYP2C9 substrates with narrow therapeutic index

CYP2B6 substrates with narrow therapeutic index			
cyclophosphamide*	efavirenz	ifosfamide*	methadone
thiotepa*	procarbazine*		
CYP2C9 substrates with narrow therapeutic index			
warfarin	acenocoumarol		
*Chemotherapeutic agents are generally prohibited.			

Table 14-7 List of prohibited antifungal and antibiotic agents

Prohibited antifungal and antibiotic agents			
ciprofloxacin	clarithromycin	erythromycin	fluconazole
Itraconazole	ketoconazole	miconazole	posaconazole
telithromycin	troleandomycin	voriconazole	

[redacted]

14.2 Appendix 2: Eastern Cooperative Group Performance Scale

Table 14-8 ECOG (WHO) Performance Status

Grade	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, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken et al (1982).

14.3 Appendix 3: Seven-Day Modified Myelofibrosis Symptom Assessment Form v2.0

Instruction to patients:

Please answer all questions to the best of your ability, based on your memory **over the past 7 days (1 week)**. There is **no right or wrong** answer.

Symptoms	Intensity Scale
1. During the past 7 days, how severe were your worst night sweats (or feeling hot or flushed) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
2. During the past 7 days, how severe was your worst itchiness due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
3. During the past 7 days, how severe was your worst abdominal discomfort (feel uncomfortable, pressure or bloating) due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
4. During the past 7 days, how severe was your worst pain under the ribs on the left side due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
5. During the past 7 days, what was the worst feeling of fullness (early satiety) you had after beginning to eat, due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
6. During the past 7 days, how severe was your worst bone or muscle pain due to MF (diffuse, **not** joint or arthritis pain)?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
7. During the past 7 days, what was the worst degree of inactivity (including work and social activities) you had due to MF?	0 (Absent) 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Note: The questionnaire provided here is a sample for information purposes only. Paper questionnaires for patient completion in the study will be provided by Novartis to be used as source documents.

[redacted]

14.4 Appendix 4: EORTC QLQ C-30

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year):

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

[redacted]

During the past week:	Not at all	A little	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

[redacted]

14.5 Appendix 5: MDRD-eGFR Formula

$$\text{Glomerular filtration rate (mL/min/1.73 m}^2) = 170 \times [\text{serum creatinine (mg/dL)}]^{-0.999} \times [\text{age}]^{-0.176} \times [\text{urea nitrogen (mg/dL)}]^{-0.170} \times [\text{albumin (g/dL)}]^{+0.318} \times (0.762 \text{ if female}) \times (1.180 \text{ if black})$$

14.6 Appendix 6: Hepatic encephalopathy grading according to West Haven Criteria

Grade	Symptoms
1	Trivial lack of awareness; Euphoria or anxiety; Shortened attention span; Impaired performance of addition or subtraction
2	Lethargy or apathy; Minimal disorientation for time or place; Subtle personality change; Inappropriate behavior
3	Somnolence to semi-stupor, but responsive to verbal stimuli; Confusion; Gross disorientation
4	Coma (unresponsive to verbal or noxious stimuli)

Source: Ferenci et al (2002).

[redacted]

[redacted]