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Oncology Clinical Development & Medical Affairs

INC424

Clinical Study Protocol CINC424A2201

A Phase Ib, open-label, dose-finding study of the JAK inhibitor INC424 tablets administered orally to patients with primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF) and baseline platelet counts >/= 50 x10^9/L and <100 x10^9/L

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AE	Adverse Event
ALT	Alanine Aminotransferase/Glutamic Pyruvic Transaminase/GPT
ANC	Absolute Neutrophyl Count
AST	Aspartate Aminotransferase/Glutamic Oxaloacetic Transaminase/GOT
AUC	Area Under Curve
b.i.d.	*bis in diem*/twice a day
BUN	Blood Urea Nitrogen
CDP	Clinical Development Plan
CTH	Clinical Trial Head
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
CBC	Complete Blood Count
CML	Chronic Myelogenous Leukemia
CRF	Case Report/Record Form
eCRF	Electronic Case Report/Record Form
CRO	Contract Research Organization
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
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
CYP	Cytochrome
DDS	Dose-Determining Set
DLT	Dose Limiting Toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
[redacted]	[redacted]
EOT	End Of Treatment
EPO	Erythropoietin
ET	Essential Thrombocythemia
EWOC	Escalation With Overdose Control
FDP	Fibrinogen Degradation Products
FPFV	First Patient First Visit
GCSF	Granulocyte Colony Stimulating Factor
GI	Gastrointestinal
hCG	human Chorionic Gonadotropin
IB	Investigator Brochure
ICF	Informed Consent Form
i.v.	Intravenous(ly)
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMS	Integrated Medical Safety
IN	Investigator Notification
INR	International Normalized ratio

IRB	Institutional Review Board
IRT	Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System
IWG	International Working Group,
[redacted]	[redacted]
[redacted]	[redacted]
LPLV	Last Patient Last Visit
LPFV	Last Patient First Visit
MAP	Master Analysis Plan documents project standards in the statistical methods which will be used within the individual clinical trial RAP documentation.
MDRD-eGFR	Modification of Diet in Renal Disease estimated Glomerular Filtration Rate
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis
[redacted]	[redacted]
MPN	Myeloproliferative Neoplasm
MTD	Maximum Tolerated Dose
MSSD	Maximum Safe Starting Dose
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NYHA	New York Heart Association
NONMEM	Non-linear Mixed Effects Modeling
o.d.	*omnia die*/once a day
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamic
PET-MF	Post Essential Thrombocythemia Myelofibrosis
PHI	Protected Health Information
PK	Pharmacokinetic
PLT	Platelet
PMF	Primary Myelofibrosis
p.o.	*per os*/by mouth/orally
PPV-MF	Post Polycythemia Vera Myelofibrosis
[redacted]	[redacted]
PTT	Partial Thromboplastin time
PV	Polycythemia Vera
q.AM	Every morning
q.PM	Every afternoon
[redacted]	[redacted]
RAP	The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses
REB	Research Ethics Board
SAE	Serious Adverse Event
[redacted]	[redacted]
SOP	Standard Operating Procedure
SSF	Screening Symptom Form
STAT3	Signal transducer and activator of transcription 3
SUSARs	Suspected Unexpected Serious Adverse Reactions
TPO	Thrombopoetin
ULN	Upper Limit of Normal
WBC	White Blood Cell

WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (eg: q28 days)
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 drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug."
Investigational treatment	Drugs whose properties are being testing 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 within approved indication/dosage
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an Interactive Response Technology
Other study treatment	Any drug administered to the patient as part of the required study procedures that was not included in the investigational treatment
Patient number	A number assigned to each patient who enrolls in the study. When combined with the investigative site number, a unique identifier is created for each patient in the study
Period	A subdivision of the study timeline; divides stages into smaller functional segments such as screening, titration, etc.
Patient withdrawal	Point/time when the patient exits from the study; at this time all study drug administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
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.
Stage in cancer	The extent of a cancer in the body. Staging is usually based on the size of the tumor, whether lymph nodes contain cancer, and whether the cancer has spread from the original site to other parts of the body
Stop study participation	Point/time at which the patient come in for a final evaluation visit or when study drug is discontinued whichever is later
Study drug	Any drug administered to the patient as part of the required study procedures; includes investigational drug and any combination or control drug(s)
Study treatment	Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins. In specific examples where it is important to judge study treatment relationship relative to a drug component of a combination treatment, study treatment in this case can refer to a drug component
Study drug discontinuation	Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of patient withdrawal
Variable	Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints

Amendment 4

Amendment rationale

As of 20 January 2015, which is the data cut off for the planned interim analysis, a total of 58 patients have been screened. Of the 58 patients screened, 46 patients started study treatment and 12 patients were declared as screen failures. The study consisted of a dose escalation phase and a safety expansion phase, and 2 different Stratums to which patients were assigned based on their platelet counts at baseline. In Stratum 1 (for baseline PLT counts of < 100 x 109/L and ≥ 75 x 109/L), 24 patients were enrolled into the dose escalation phase and 3 patients were enrolled into the safety expansion phase for a total of 27 patients. Of the 27 patients in Stratum 1, 9 patients in the dose escalation phase and 3 patients in the safety expansion phase were evaluated at the maximum safe starting dose (MSSD) of 15 mg BID. In Stratum 2 (for baseline PLT counts of < 75 x 109/L and ≥ 50 x 109/L), 15 patients were enrolled into the dose escalation phase and 4 patients were enrolled into the safety expansion phase for a total of 19 patients. Of the 19 patients in Stratum 2, 9 patients in the dose escalation phase and 4 patients in the safety expansion phase were evaluated at the MSSD of 10 mg BID. After the planned interim analysis cut off, as of 28 July 2015, no additional patients have been enrolled into the safety expansion in Stratum 1, and 2 additional patients have been enrolled into the safety expansion in Stratum 2.

The MSSD declaration of 15 mg BID for Stratum 1 was based on the occurrence of protocol-defined dose limiting toxicities during the first cycle (28 days) of treatment. However, observations from the planned interim analysis indicated that patients who started treatment at the 15 mg BID MSSD dose subsequently experienced frequent dose reductions after the first cycle of treatment. A majority of the patients who had dose reductions eventually continued study treatment at the 10 mg BID dose or lower. Additionally, a relevant clinical benefit was observed across all starting dose levels, including those who started treatment at the 10 mg BID dose levels. These observations warrant further exploration of the 10 mg BID dose level as the starting dose in Stratum 1 for myelofibrosis patients with platelet counts of < 75 x 109/L and ≥ 50 x 109/L.

Therefore, the purpose of this amendment is to revise the starting dose to 10 mg BID, from the current starting dose of 15 mg BID, and is applicable for all new patients entering the safety expansion phase of Stratum 1.

Following the approval of Amendment 4, new patients enrolled to Stratum 1's safety expansion phase will begin treatment with ruxolitinib at 10 mg BID. In line with the original sample size specification for the MSSD cohorts, approximately 20 patients in total will be enrolled into 10 mg BID, inclusive of those already enrolled at the 10 mg BID dose level in Stratum 1. Recruitment into the study will continue until approximately 20 patients are enrolled at this dose level into stratum 1 OR the Last Patient's First Visit (LPFV) will occur on 01 September 2017, whichever comes first. Patients already taking the 15 mg BID dose in Stratum 1's safety expansion phase will continue to take their assigned dose.

Stratum 2 will remain unchanged and maintain its original enrollment requirement of 10 patients at the MSSD.

Other changes to the protocol include the following:

- The safety and tolerability data from the interim analysis confirmed that the tolerability of ruxolitinib in the observed low-platelet myelofibrosis patients and at the dose levels evaluated in this study were consistent with the known safety profile of ruxolitinib in the general myelofibrosis population. No new or unexpected safety signals were observed. Therefore, the clinic visits have been reduced and all lab-only visits have been eliminated to significantly reduce patient burden.
- [redacted]
- United Kingdom patients with no current alternative access to drug outside the study are allowed to continue on study treatment beyond 3 years of treatment on study until up to 3 years beyond the LPFV.
- [redacted]
- The requirement for male contraception has been removed to align with the updated Investigator Brochure for ruxolitinib (Edition 13).
- Section 6.1.4 Discontinuation of Study Treatment has been revised to now include a comprehensive compilation of all criteria requiring study treatment discontinuation, as previously included in the protocol. No new discontinuation criteria have been added in Amendment 4.

Changes to the protocol

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

The following sections have been changed:

- List of Abbreviations: added LPFV, last patient first visit
- Section 1.2: updated overview of ruxolitinib based on standard program language
- Section 3.1, 5.1.2.5, 9.8: Updated study design to reflect the new dose for Stratum 1 as 10 mg BID and to reflect the requirement to enroll approximately 20 patients at this dose, or enroll the last patient by 01 Sept 2017, whichever comes first
- Section 3.1.3 & 3.8: Updated treatment duration to reflect that UK patients may continue on study treatment past Week 156 and until LPFV plus 156 weeks
- Section 3.8: Added that study treatment is commercially available and reimbursable for patients completing study treatment, with the exception of the UK which has a specific alternative available for continued access to treatment for patients.
- Section 4.2: Updated exclusion criteria #2 to remove requirement for male contraception per updated safety guidance for the INC424 program
- Section 6.1: Updated list of Visit Evaluation Schedule tables
- Table 6-1, 6-2, and 6-3, Section 6.1.3: Updated to reflect revision of Visit Evaluation Schedule as follows: study visits in first 8 weeks will be reduced to every 2 weeks, all lab-

only visits removed, UK patient visits past week 156 added and only summary pages to be entered

- Section 6.1.4: Section added per new protocol template to consolidate all reasons for treatment discontinuation in one section
- Section 6.1.4.1 Criteria for patient withdrawal section deleted and included in 6.1.4
- Section 6.1.4.1.1 Follow up for toxicities section deleted and included in 6.1.4
- Section 6.1.4.2 re-labelled to 6.1.4.1 as Replacement Policy
- Section 6.1.5: Follow up for safety evaluations section updated per standard language
- Section 6.1.6: Lost to follow up section added per standard protocol language
- Section 6.1.7: Withdrawal of consent section added per standard protocol language
- Section 6.2.1, 6.2.2 and subsections, 6.2.4.3: updated table numbers to Table 6-1, 6-2, 6-3
- Table 6-7 re-numbered as Table 6-4: sample collection time windows for pop PK
- [redacted]
- [redacted]
- [redacted]
- Section 8.4: remove lab-only visit language
- Section 9.8: revised sample size calculation to include additional patients required to evaluate 10 mg BID in approximately 20 patients
- Appendix 3: updated contraception language per standardized INC424 program language

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

Amendment 3

Amendment rationale

The primary reason for this amendment is to continue to follow and to collect 3 years of safety data on this low- platelet MF population. All safety assessments will remain as original protocol for the Core study period of 168 Days. After 168 Days patients will enter into the Extension period of the study where safety and efficacy parameter of spleen length will be collected with reduced frequency as follows:

- Clinical visits to the research site every 12 weeks as is consistent with clinical practice
- Safety lab every 6 weeks (lab may be drawn locally as permitted by local laws)

Other changes to the protocol include:

- Remove pharmacokinetic (PK) assessments for patients in the Safety Expansion Phase as there is sufficient patient PK sampling to characterize the pharmacokinetics of INC424 in this patient population with Stratum 1 currently at dose level 5 and Stratum 2 currently at dose level 3.
- Based on clinical experience on study to date and feedback from the investigators allow, at the discretion of the physician, re-escalation of study drug to the dose where platelet counts first declined and dose reduction occurred and re-start- up of the study drug to the dose where platelet counts first declined.
- Due to the extended timeline of the study, an interim analysis and Clinical Study Report is planned when the MSSD is declared for both strata and all patients in the Dose escalation phase have completed the core study period or discontinued.
- Under Table 5-4 (Criteria for interruption and re-initiation of INC424 treatment), in the sub-category for 'Other adverse events', it was not the intent of dose modification guidelines to HOLD the dose for Grade 2 -3 events, that were assessed as 'not related' to study drug. Therefore, the recommendation to hold the study drug for grade 2-3 events that were not related to INC424 was removed.
- [redacted]

Study Status:

As of the 5th September 2013, 32 patients have been enrolled to treatment; the first patient was screened on 16 March 2011 and the first patient treated on 17 June 2011. The first cohort of three patients has just completed Stratum 1 at Dose Level 5, (15mg BID and highest dose level), with no DLTs and the stratum is now being expanded to include an additional 6 patients with the purpose to confirm the MSSD for this stratum. In Stratum 2, there was one DLT of thrombocytopenia at Dose Level 3 (10 mg BID) and this cohort has been expanded to an additional 3 patients and a Dose Escalation meeting is planned early September 2013.

Changes to the protocol

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

The following sections have been changed:

- Section 3.1 Study design
- Section 3.1.3 Treatment duration
- Section 3.3 Purpose and timing of interim analyses/design adaptations
- Section 3.8 Definition of End of the study
- Section 5.1.4 Treatment interruption and treatment discontinuation and Table 5-4Criteria for interruption and re-initiation of INC424 treatment – Recommended dose modifications
- Section 6.1 Study flow and visit schedule: Table 6-1 : Visit Evaluation Schedule and Table 6-2: Laboratory Assessment Schedule
- Section 6.1.3 Treatment period
- Section 6.1.4. End of treatment and withdrawal visit
- Section 6.2.2.7 Cardiac assessments
- Section 6.2.3.2 Pharmacokinetic blood sample collection and handling
- [redacted]
- Section 9: Statistical methods and data analysis
- [redacted]
- Section 9.7 Interim analysis

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.

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Amendment 2 for the United Kingdom only

Amendment rationale

The MHRA has requested a change to the major rationale of Amendment 1 to remove the wording 'until ruxolitinib is commercially available' as this is not an acceptable treatment end-point. A specified length of treatment is an acceptable end-point and this has been provided.

The rationale for the length of study treatment for Amendment 1 is as follows:

- To extend the treatment period for patients benefiting from the study drug after the Study Day 168 visit.
- If based on investigator's judgment patients are benefiting from treatment, these patients will be able to continue on the study until 30 June 2013 or until the patients have access to study drug through commercial supplies [if applicable by local regulations], whichever comes first.
- The 30 June 2013 date may be re-evaluated in case the drug is not commercially available at that time, and an amendment will be issued to extend the treatment duration.

The above rationale for the length of study treatment for Amendment 2 will read as follows for the United Kingdom only:

- To extend the treatment period for ongoing patients benefiting from the study drug after the Study Day 168 visit.
- All patients will be treated until LPFV plus 168 days; the minimum treatment duration for any patient will therefore be 168 days if the patient is not permanently discontinued for other reasons e.g. adverse event.
- The treatment duration may be re-evaluated at that time, and an amendment issued to extend the treatment duration.

Study status

Fifteen patients have been screened for this study. Six patients were enrolled and nine patients were screen failures. Two of the enrolled patients have discontinued treatment.

Changes to the protocol

The following sections have been changed:

Section 3.1, Section 3.1.3, Section 3.8, Section 6.1.3, and Section 6.1.4: Treatment endpoint revised to LPFV plus 168 days

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

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

The changes described in this amended protocol require IRB/IEC approval prior to implementation. In addition, if the changes herein affect the Informed Consent, sites are

required to update and submit for approval a revised Informed Consent that takes into account the changes described in this amended protocol.

Amendment 1

Amendment rationale

The rationale for the amendment is as follows:

- To extend the treatment period for patients benefiting from the study drug after the Study Day 168 visit.
  - If based on investigator's judgment patients are benefiting from treatment, these patients will be able to continue on the study until 30 June 2013 or until the patients have access to study drug through commercial supplies [if applicable by local regulations], whichever comes first.
  - The 30 June 2013 date may be re-evaluated in case the drug is not commercially available at that time, and an amendment will be issued to extend the treatment duration.
- To re-evaluate the inclusion & exclusion criteria to the study:
  - New safety data from [CINC424A2352] and the [INCB 1824-351] trials provided further information on the safety of treating patients with low platelet values with INC424. Therefore some inclusion & exclusion criteria are no longer necessary.
  - Fluctuation in the platelet count inherent to the nature of the disease has precluded potential patients' qualification in the study. Therefore the qualifying platelet criteria have been revised.
  - Inclusion & exclusion criteria were too strict, therefore hampering patients' accrual.
- Definition of disease progression will be amended to be in line with the most current [CINC424A2352] trial version.
- Other non major changes are included in this amendment.
- Extend the patient treatment duration. The following items were reviewed:
- Study duration: amended to provide the drug to patients benefiting from the study drug until 30 June 2013 or until the patients have access to study drug through commercial supplies [if applicable by local regulations], whichever comes first. The 30 June 2013 date may be re-evaluated in case the drug is not commercially available at that time, and an amendment will be issued to extend the treatment duration.
- Conditions to continue in the extension period: all patients who are benefiting from study drug will have the option to continue the study treatment unless at least one withdrawal criteria is met and only if the treatment with INC424 is considered the patient's best therapeutic option by the Investigator. Patients must have completed the Study Day 168 visit.
- Conditions for maximum intra-patient dose escalation after the Study Day 168 visit. Each patient may be treated at the higher of:
- the MSSD level established for that stratum or
- 10 mg bid. 10 mg bid dose has been selected as this is the lowest dose which has shown efficacy in the completed Phase III [INCB 1824-351] study and because the safety profile

for patients experiencing a thrombocytopenic event has been shown as safe for escalation to this dose level.

- Additional patients' visits: Study Day 196, 224, 252, 280, 308, 336 and every 56 days thereafter.
- Additional patient withdrawal reason: the patient has completed at least Study Day 168 and the INC424 treatment is available through commercial supplies [if applicable by local regulations].
- Study end: study treatment will continue until 30 June 2013 or until the patients have access to study drug through commercial supplies [if applicable by local regulations], whichever comes first.
- Deletion of the wording premature as there is no fixed end for the study. Patients can still be discontinued or withdrawn, but this is not premature to a timepoint.
- Specification for the pharmacodynamics: samples will be collected at the Screening visit and at Study Days 1, 15, 29, 57, and 168 (or at the End of Treatment if before the Study Day 168 visit).
- [redacted]
- Core and addendum CSR: the core clinical study report will be based on a data cut-off corresponding to the earlier time of: the last on-treatment patient's Day 168 visit or End of Treatment visit. An addendum to the core clinical study report will be provided at the completion of the study to summarize and list the additional safety and efficacy data as appropriate.
- Modify the definition of the baseline PLT count which will qualify the patient for the study:
- The platelet count value needs to be within the permitted range at Screening OR at Day 1 to qualify the patient for enrolment in the respective stratum. Considering fluctuations of the PLT count for this particular patient population, one value is sufficient to qualify a patient into a specific stratum.
- A platelet count re-test is authorized at Screening but will need to be conducted within 13 days. All laboratory parameters are allowed to be re-assessed at Screening to confirm the eligibility of the patients.
- Clarification that screening and re-screening are allowed once for each stratum.
- Clarification of the stratum selection in case the screening PLT count and Day 1 PLT count values qualify the patient in two different strata: the PLT value at the Day 1 will determine the choice of the stratum.
- Modify the inclusion criteria related to coagulation parameters, neutrophil parameters, the use of the previous MF treatment, clarify the weight loss decrease timeframe:
- Coagulation parameters: INR and PTT increased from 1.2 x ULN to 1.5 x ULN based on the observation that eligible patients may have slightly elevated coagulation parameters as per information from the recently completed Phase III [INCB 1824-351] study and because bleeding risks are low below this threshold.

- Deletion of the fibrinogen and D-dimer or fibrinogen degradation products (FDP) criteria no longer required to qualify a patient in the study. There is no clear evidence that these particular cut-off values correlate with the risk of bleeding.
- Neutrophil parameters: ANC allowed value decreased to 1 x 10^9/L at Screening as per other INC424 studies.
- Discontinuation of prior MF therapy decreased to 7 days prior to Screening evaluations in order not to leave the patients without treatment for a long period of time.
- Weight loss decrease timeframe defined within the past year in order to ensure that the constitutional symptom is relevant within the study timeframe.
- Modify the exclusion criteria related to PLT transfusion exclusionary period, clarify the frequency of the use of drugs that interfere with coagulation or inhibit PLT function, clarify the bilirubin parameter check, clarify the stem cell transplantation option, delete the ulcerative diseases as a gastrointestinal function impairment, replace the word coagulopathy by bleeding diathesis and addition of an exclusion criterion related to the patient life expectancy:
- PLT transfusion exclusionary period decreased to 14 days prior to Screening evaluations, in order to palliate any urgent needs and since the half-life of a platelet transfusion is approximately one week.
- Only regular use of drugs that interfere with coagulation or inhibit PLT function are prohibited in the study. The investigator will assess the regularity of use of such agents versus occasional use. Selective COX-2 inhibitors and acetaminophen deleted from the list of prohibited medication as these drugs do not affect coagulation or platelet functions. Clarify that low dose aspirin (≤ 125 mg/day) is allowed. Clarify that medications used for myelofibrosis are prohibited during the treatment period but are allowed during the 30-day follow-up period after the End of Treatment.
- Bilirubin parameter checks defined as per normal practice: total bilirubin to be assessed first and if the value is more than 2 x the ULN, investigator to assess the direct bilirubin level.
- Stem cell transplantation option reviewed to exclude only patients who are candidates for the transplantation.
- The ulcerative diseases are removed from the gastrointestinal function impairment exclusion criterion, as the diseases and the associated concomitant medications do not impact the absorption of the study drug which is quick and almost complete.
- Replacement of wording coagulopathy which describe the hyper- and hypocoagulation by bleeding diathesis which is relevant for the study.
- Addition of life expectancy exclusion criterion.
- Progression as defined by an increase in spleen size by palpation has been amended to an increase of >40% to align with the definition in [CINC424A2352] study. Study [CINC424A2352] defines progression as an increase >25% spleen volume by MRI which approximately correlates to >40% by palpation.
- [redacted]

[redacted]

- Clarify that the study drug label does not include a medication number.
- Deletion of redundant Section 6.2.4.1.3 regarding the pharmacodynamic analysis already captured in the statistical Section 9.5.5.2.
- Clarify that the approximate number of patients planned to be enrolled in the Dose-Determining Set (DDS) for this study is 62. The maximum number of patients to enroll cannot be predicted as it will depend on the dose escalation and the DLTs which will occur.
- Modify the Laboratory-only visit which can be done at the clinic site or at any local laboratory provided that the investigators review the results within 2 business days.
- Amend the Table 5-5 to reflect that the Dose escalation guidelines described in the table refer to thrombocytopenia events except grade 4 events, which are described in Table 5-6.
- Other changes not specified above are only editorial in nature (i.e. typos).

Study status

Three patients have screen failed in the study, but no patient has started the treatment.

Changes to the protocol

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

The following sections have been changed:

- Section 3.1, 3.1.3, 3.8, 3.9, 5.1.2.7, 6.1, 6.1.3, 6.1.4, 6.1.4.1, 6.1.4.2, 6.1.5, 6.2.1, 6.2.2.7.1, [redacted], 6.2.4.3, 8.4, 9, [redacted] 9.7, Table 6-1 and 6-2: extension of the study.
- Section 4.1 (inclusion criterion 6), 6.1.1, 6.1.1.1, 6.1.1.3, 9.2, 9.5.1, [redacted] definition of the baseline PLT count which will qualify the patient for the study.
- Section 4.1 (inclusion criteria 3, 6, 7 and 10): inclusion criteria related to the coagulation parameters, the neutrophil parameters, the use of the previous MF treatment.
- Section 4.2 (exclusion criteria 4, 6, 7, 8, 12, 13 and 22, and Section 5.1.10): exclusion criteria related to PLT transfusion exclusionary period, clarify the bleeding history timeframe, the frequency of the use of drugs that interferes with coagulation or inhibits the PLT function, the bilirubin parameter check, the stem cell transplantation option and addition of an exclusion criterion related to the patient life expectancy.
- Section 6.1.4.1. & 6.2.1: increase spleen size percentage has been changed to meet criteria for progression.
- [redacted]
- Section 5.2.3: clarification regarding the study drug label.
- 6.2.4.1.3: deletion of redundant information.
- 3.1, 9.8 and Appendix 13: approximate number of patients to enroll.

- 6.1.3 and 6.2.2.5: Laboratory-only visits.
- Table 5-5: dose escalation guidelines following thrombocytopenia different than grade 4 events.

IRB/IEC

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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, MF 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.

The median age at diagnosis is approximately 60 to 65 years. The incidence of PMF has been estimated at 1.5 cases per 100,000 people. Survival in MF varies with the presence or absence of specific risk factors. (Cervantes et al 2009) have recently published a multi-center analysis of risk factors and their impact on prognosis in patients with MF. They identified age of 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 (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 as individually predictive of outcome. They demonstrated that patients could be distinctly grouped into four categories without overlapping median survival curves based upon their number of risk factors (Table 1-1).

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

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, although with substantial (10-20%) risks of mortality, (Deeg et al 2003). 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. Splenectomy, performed in approximately 10% of the patient cohort reported by (Cervantes et al 2009), is associated with significant morbidity and mortality. Splenic irradiation is also 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 et al 2009), is considered to be an adverse risk factor by the Mayo Clinic group, (Elliott et al 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, whose DLT is thrombocytopenia, and potentially other treatments. Therefore, thrombocytopenic patients are often excluded from investigational studies despite having MF requiring therapy.

1.2 Overview of INC424 (ruxolitinib)

INCB018424 phosphate, designated INC424 throughout, is a novel, potent, reversible and selective inhibitor of JAK1- and JAK2-STAT signaling (Quintas-Cardama et al 2010) that is currently under development for treatment of MPNs and advanced hematologic malignancies.

Ruxolitinib is currently approved under the trade name of 'Jakavi' in over 80 countries including the EU and Canada where it is indicated for the treatment of disease-related splenomegaly or symptoms in adult patients with (primary myelofibrosis) PMF, post-polycythemia vera myelofibrosis (PPV-MF) and post-essential thrombocythemia myelofibrosis (PET-MF). Jakavi is currently under review by health authorities worldwide for the treatment of PV patients who are resistant to or intolerant of hydroxyurea, based on the results of the RESPONSE pivotal study. This second indication has already been approved in the EU and in some other rest of the world countries. Ruxolitinib is also approved in the USA under the trade name of 'Jakafi' and is indicated for the treatment of patients with intermediate or high risk myelofibrosis, including PMF, PPV-MF and PET-MF and for the treatment of PV patients who have had an inadequate response to or are intolerant of hydroxyurea.

1.2.1 Preclinical studies

[redacted]

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

1.2.2 Clinical pharmacology of INC424

Following oral, single-dose administration of INC424 capsules in the fasted state, INC424 was absorbed rapidly, typically attaining peak plasma concentrations within 1 to 3 hours after administration for all doses. After attaining C_{max}, the INC424 plasma concentrations declined with a mean terminal-phase disposition $t_{1/2}$ of approximately 3-5 hours. The mean INC424 C_{max} and AUC increased with approximately linear proportionality to dose for the entire dose range evaluated of 5 to 200 mg. There was no significant food effect on absorption or exposure. The double-blind, randomized, placebo-controlled, single dose escalation study [INCB 18424-131] was conducted to investigate the food effect. T_{max}, C_{max}, AUC in particular were determined. The main conclusion was that overall magnitude of the food effect on the INC424 exposure is not expected to be clinically significant.

INC424 is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isozyme. Systemic exposure of INC424 was appreciably increased (AUC 2-fold higher) when given in combination with ketoconazole, a potent CYP3A4 inhibitor, with a similar effect observed on the pharmacodynamic (PD) activity (cytokine-induced STAT3 phosphorylation). CYP3A4 inducers significantly decreased the exposure to INC424, with essentially no difference observed on the PD activity (cytokine-induced STAT3 phosphorylation). [redacted]

INC424 was given as a single 25 mg dose to patients with varying degrees of renal function, [INCB 18424-142] study, and to patients with varying degrees of hepatic dysfunction or with normal hepatic function, [INCB 18424-137] study. Mild, moderate or severe impairment of renal function had no statistically significant effect on PK or PD parameters; patients

requiring dialysis showed prolonged PD activity without a demonstrable effect on INC424 clearance. In patients with mild, moderate and severe hepatic impairment, the mean total AUCs of INC424 were 88%, 29% and 66% higher, respectively, compared to patients with normal hepatic function. Terminal half-life of INC424 was increased in patients with hepatic impairment by approximately 2-fold compared to healthy controls. The patients with severe hepatic impairment showed modestly protracted PD activity compared to the other hepatically impaired patients who displayed PD activity similar to the healthy controls.

Additional details as to the clinical pharmacology of INC424 may be found in the IB.

1.2.3 INC424 clinical safety in healthy volunteers

INC424 has been administered in single or multiple doses to over 200 healthy volunteers. In single dose studies, INC424 has a well established safety profile and has been well tolerated with Adverse Events (AEs) generally mild in intensity, reversible and of similar incidence following INC424 treatment compared with placebo or with other control treatments.

In a 10-day multiple dose study, a total of 71 healthy volunteers in 6 cohorts received doses of 50 mg qd, 100 mg qd, 15 mg b.i.d., 25 mg b.i.d. or 50 mg b.i.d. INC424 or placebo, [INCB 18424-132] study. INC424 was well tolerated in the study, with most AEs reported equally by both INC424-treated and placebo-treated volunteers. Neutropenia was noted in 3 volunteers receiving the highest dose of INC424, 50 mg b.i.d. 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 b.i.d. 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 b.i.d. and 100 mg qd were determined to be the maximum tolerated doses (MTDs) in this study based on the dose limiting toxicity (DLT) of neutropenia.

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.

For additional details related to studies conducted in healthy volunteers, consult the IB.

1.2.4 INC424 clinical safety and efficacy in myelofibrosis patients (Phase I/II study)

Study [INCB 18424-251] is an ongoing Phase I/II open label study of INC424 in patients with PMF, PPV-MF or PET-MF in patients with baseline platelet counts of at least 100 x 10^9/L. A total of 154 patients have been enrolled and treated at twice daily dose regimens of 10 mg b.i.d. to 50 mg b.i.d., or once daily regimens of 25 mg qd to 200 mg qd. Patients enrolled since August 2008 have had individually titrated dose regimens that begin at doses of 10 mg b.i.d., for patients with baseline platelets 100 x10^9/L - 200 x10^9/L, or 15 mg b.i.d., for patients with baseline platelets > 200 x10^9/L, with intra-patient dose escalation allowed up to doses of 20 mg b.i.d. or 25 mg b.i.d., respectively.

Efficacy data from this study demonstrate marked and durable reductions in spleen size which has been measured as palpable length below the left costal margin. Twice daily regimens were associated with a prompt decrease in spleen size; the reduction in spleen length appears dose-dependent. The effect on decreasing spleen size was still evident after many months of continued dosing. Once daily dosing regimens also are associated with an initial, rapid decline in spleen size and show approximate dose dependence. Spleen reduction occurred regardless of presence/absence of the *JAK2*V617F mutation and independent of the MF disease subtype (PMF, post-PV MF or post-ET MF), (Verstovek et al 2010).

Progressive myeloproliferative neoplasms are associated with weight loss and cachexia, presumably due to deregulation and abnormal elevation of a variety of pro-inflammatory cytokines. In the [INCB 18424-251] study, after an initial weight loss (presumably due to the rapid decrease in splenomegaly and hepatomegaly and loss of ascites and/or pleural effusions) there was a gain in total body weight that was somewhat dose-dependent. Weight gains were present in most patients, importantly, including those with Body Mass Index (BMI) at baseline in the lowest quartile (BMI below ~ 22).

A prompt shift in the Eastern Cooperative Oncology Group (ECOG) performance scores in individuals with scores of 1 or 2 towards a score of 0 was noted in this study and this improvement was maintained over ~ 24 months.

[redacted]

In summary, INC424 was associated with prompt and marked reduction in spleen size, gains in total body weight, improvement in ECOG status performance scores and improvement in constitutional symptoms that can be debilitating in this patient population. Refer to the IB for more complete information.

INC424 has been well tolerated by this aged population with advanced disease. Most adverse events were mild to moderate in severity, considered unrelated to study drug administration and not dose dependent. Related adverse events occurring in at least 8 patients (5%) included in the safety database through December 31, 2009 were restricted to thrombocytopenia (66 patients, 43%), anemia (45 patients, 29%), weight increased (11 patients, 7%), diarrhea (10 patients, 6.5%) and fatigue (8 patients, 5%). [redacted]

Thrombocytopenia represents the DLT in the population of the [INCB 18424-251] study. Forty (40) patients (26% of study population) had a grade 3 or grade 4 decline in platelet (PLT) count during the study (31 grade 3 events, 9 grade 4 events). Patients with grade 3 or grade 4 thrombocytopenia entered the study, in general, with PLT counts less than 200 $x10^9$/L, although there are exceptions to this trend. Thrombocytopenia occurred rapidly: 20% of grade $\geq$ 3 events occurred in the first 4 weeks of dosing, just under half (48%) of grade $\geq$ 3

events occurred in the first 16 weeks of dosing (Figure 1-1). The decrease in PLT counts (expressed as median percent change from baseline) occurred almost entirely over the first 4 weeks, with additional gradual decline afterwards (Figure 1-2).

Figure 1-1 Kaplan-Meier analysis of time to 1st new or worsening grade 3 or 4 thrombocytopenia in INCB 18424-251 study

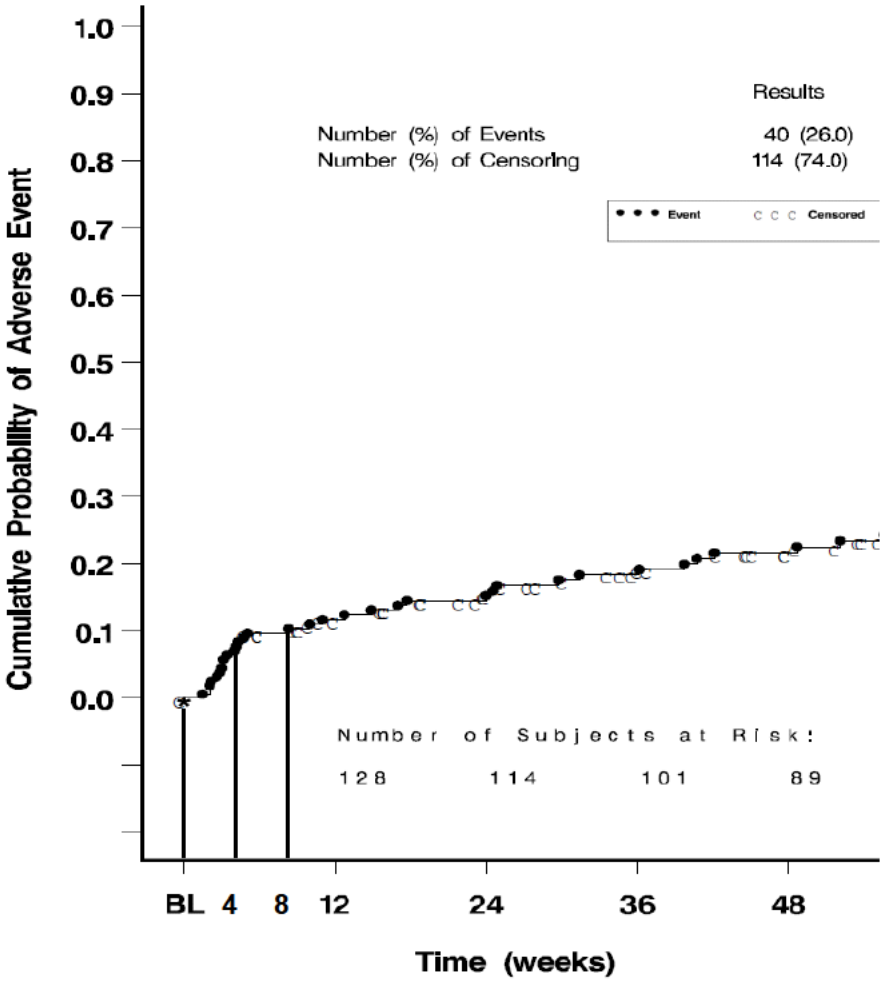
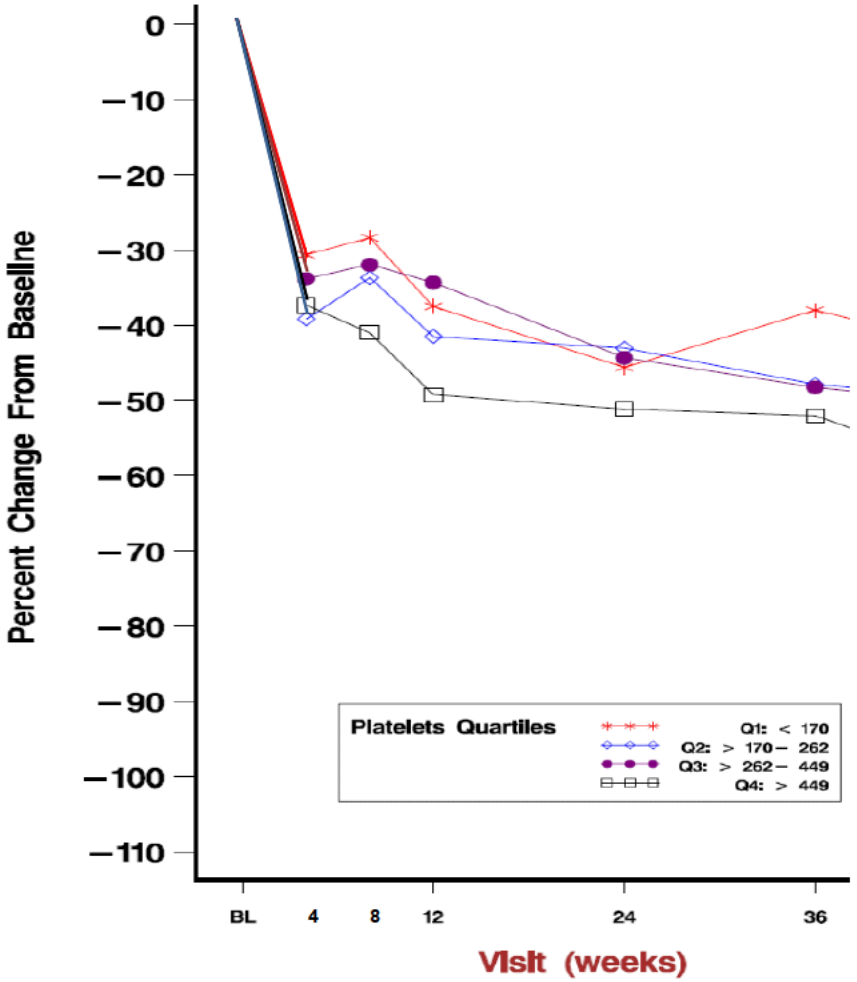


Figure 1-2 Median percent change from baseline in platelets by baseline platelets quartile in INCB 18424-251 study



Patients initially assigned to the 50 mg b.i.d. dose group had an incidence of grade 3 thrombocytopenia of 60% (3 of 5 patients) and of grade 4 thrombocytopenia of 20% (1 of 5 patients). The 25 mg b.i.d. dose group was the largest dose group examined. This dose group included patients with mean baseline PLT counts of 345 $x10^9$/L and had an overall incidence of grade ≥ 3 thrombocytopenia of 36% (17 of 47 patients); 12 patients had grade 3 events (26%), and 5 patients had grade 4 events (11%). Patients enrolled in a subsequent cohort were assigned to an initial dose of 15 mg b.i.d. provided their baseline PLT count was > 200 $x10^9$/L; the incidence of grade 3 thrombocytopenia was markedly reduced (1 of 35 patients) and there were no grade 4 events. At a starting dose of 10 mg b.i.d., there were 6 of 30 patients (20%) with grade 3 thrombocytopenia; there were no grade 4 events. Importantly, 8 of the 30 patients at a starting dose of 10 mg b.i.d. enrolled into the study under a protocol amendment specifying this dose for a baseline PLT count between 100 $x10^9$/L to 200 $x10^9$/L. Three of these patients (38%) had baseline PLT counts ranging from 119 $x10^9$/L to 156 $x10^9$/L and subsequently developed grade 3 thrombocytopenia. This accounts, in part, for the higher incidence of grade ≥ 3 thrombocytopenia in this dose group compared to 15 mg b.i.d. (Table 1-2).

For nearly all patients, thrombocytopenia was rapidly reversible and manageable with dose interruption and reduction (Section 3.4.5); low platelet count was the primary reason for study discontinuation for few patients.

Table 1-2 Incidence of thrombocytopenia in the study INCB 18424-251

Dose	10 mg b.i.d.	15 mg b.i.d.	25 mg b.i.d.	50 mg b.i.d.	25 mg qd	50 mg qd	100 mg qd	200 mg qd
No of patients	30	35	47	5	6	22	6	3
Grade 3	6 (20%)	1 (2.9%)	12 (26%)	3 (60%)	1 (17%)	6 (27 %)	2 (33%)	0
Grade 4	0	0	5 (11 %)	1 (20%)	0	2 (9.1%)	0	1 (33%)
Total Gr 3 + 4	6 (20 %)	1 (2.9%)	17 (36%)	4 (80%)	1 (17%)	8 (36%)	2 (33%)	1 (33%)

The risk of spontaneous hemorrhage in any patient as a result of thrombocytopenia generally does not become manifest until platelet counts fall below 10 to 20 $x10^9$/L (Slichter 2004). In [INCB 18424-251] study, the lowest platelet counts observed (grade 4 thrombocytopenia events) ranged from 6-22 $x10^9$/L. There was one patient with associated petechiae and no events of hemorrhage in the 9 patients with grade 4 platelet declines.

There were 2 deaths where the primary cause of death was related to hemorrhage (upper gastric and cerebral hemorrhage). In the case of upper gastric hemorrhage, the patient had emergency surgical repair of a bleeding duodenal ulcer and died of post-operative complications. The PLT count was 447 $x10^9$/L and there was a history of antecedent aspirin use and epistaxis. The event was considered unrelated to INC424. In the case of cerebral hemorrhage, the patient had normal PLT count (201 $x10^9$/L), normal coagulation tests, and a history of hypertension. The event was assessed as possibly related to INC424.

Other SAEs on study [INCB 18424-251] that involved hemorrhage of any kind have been examined. One patient was admitted to the hospital with a PLT count of 65 $x10^9$/L and ultimately required splenectomy, following which a post-operative hemorrhage was noted in the surgical drains. The patient was discharged from the hospital but chose to discontinue study drug. Another patient had 2 episodes of lower gastrointestinal hemorrhage that were assessed as unrelated to INC424. No information about PLT counts during the course of the event is provided. A patient suffered from gastrointestinal hemorrhage of unknown source with a PLT count of 510 $x10^9$/L. One patient had hematuria due to prostatic surgery; the PLT count was 1,636 $x10^9$/L. Another patient suffering from splenomegaly developed an intra-abdominal hematoma adjacent to the spleen, with a PLT count of 99 $x10^9$/L. One patient was hospitalized for melena with a PLT count of 93 $x10^9$/L.

Because of the advanced disease present in many of the participants in study [INCB 18424-251], there are a number of SAEs that have been reported that were assessed as unrelated to study drug. Of related SAEs reported in the study to date, the most frequent are those reflecting inhibition of bone marrow function(s) (i.e. thrombocytopenia) and activation of inflammatory cytokines when the inhibitory influence of INC424 is removed due to drug interruption or discontinuation. See the IB for complete details on INC424 clinical study findings.

1.3 Study purpose/rationale

For a significant population of thrombocytopenic MF patients there are limited data about the safety of INC424 or what might be an appropriate dose, since in all studies conducted to date with INC424, baseline PLT count of ≥ 100 x10^9/L has been an inclusion criterion. However, thrombocytopenia is a frequent event in MF; as per epidemiology data (Mesa et al 2007), 16.5% of all MF patients are reported to have PLT counts < 100 x10^9/L at diagnosis, while in the intermediate risk-1, -2 or high-risk disease population the incidence of thrombocytopenia is estimated by medical experts to be higher. A previous phase I/II study, [INCB 18424-251], has established thrombocytopenia as the DLT of INC424 in MF patients with a MTD of both 25 mg b.i.d. and 100 mg qd. The incidence of grade ≥ 3 thrombocytopenia in this phase I/II trial was 20% at 10 mg b.i.d., 2.9% at 15 mg b.i.d. and 36% at 25 mg b.i.d. As noted in above (Section 1.2.4), the higher incidence of grade ≥ 3 thrombocytopenia in the 10 mg b.i.d. dose group compared to 15 mg b.i.d. one can be partially explained by the more frequent presence of patients with low baseline PLT counts in the former dose group compared to the latter one. Data from the same trial show that patients who entered the study with baseline PLT counts 100-150 x10^9/L developed grade ≥ 2 thrombocytopenia more frequently (75% vs. 37%, respectively, for the most commonly used doses that will be relevant to this trial, 10 mg b.i.d. and 15 mg b.i.d.) compared with patients with baseline PLT counts > 150 x10^9/L, although with a similar nadir (grade 2 and 3). Thrombocytopenia occurred rapidly (Figure 1-1 and Figure 1-2), and resolved with drug interruptions or dose decreases (Section 3.4.5). [redacted] In [INCB 18424-251] study, some patients continued to receive INC424 while their platelet count ranged between 50 and 100 x10^9/L (for details, see Section 3.4.5), but no patients with platelet counts below 100 x10^9/L have initiated INC424 therapy, and therefore the MTD for patients with low platelets needs to be directly established.

The purpose of this phase Ib clinical trial is to directly evaluate the safety of INC424 in the low-PLT MF population and to establish the Maximum Safe Starting Dose (MSSD). The phase I/II [INCB 18424-251] study of INC424 in MF, provides evidence that there may be a subset of thrombocytopenic MF patients who could tolerate INC424 doses higher than the MSSD that will be established in this study. Moreover, in the phase III, [INCB 18424-351] and [INCB 18424-352] trials in MF, INC424 was used at a starting dose that was subject to further escalation. Based on this rationale, this study will attempt to identify a safe starting dose for thrombocytopenic MF patients. Further dose escalation beyond the MSSD, for additional clinical benefit, although not tested in this study, may be feasible in selected MF patients presenting with thrombocytopenia and could be explored in another clinical trial.

Preliminary data of efficacy in addition to pharmacokinetic data will be obtained. The starting dose will be 5 mg b.i.d., lower than the 15 mg b.i.d. used in the phase III MF trials. Since the incidence of grade ≥ 3 thrombocytopenia in the [INCB 18424-251] study was 36% at 25 mg b.i.d., the maximum dose in the current study will be 15 mg b.i.d., if MSSD is not reached at a lower dose. Initially, only patients with PLT counts 75-99 x10^9/L (first stratum) will be enrolled. Once safety in patients in the first stratum is established at the first two dose levels (5 mg b.i.d.; 5 mg q.AM / 10 mg q.PM) the eligible population will be further expanded to patients with PLT counts 50-74 x10^9/L (second stratum).

2 Objectives and endpoints

2.1 Study objectives

Primary

- To establish the MSSD of INC424 in patients with MF and baseline PLT count < 100 x 10^9/L and ≥ 75 x 10^9/L (first stratum) and PLT count < 75 x 10^9/L and ≥ 50 x 10^9/L (second stratum)

Secondary

- **Safety:** To characterize the safety of INC424
- **Pharmacokinetics:** To characterize the pharmacokinetics of INC424 in this patient population
- **Pharmacokinetic-pharmacodynamic relationship:** To characterize the pharmacokinetic-pharmacodynamic relationship of this population
- **Efficacy:** To obtain estimates of efficacy

Exploratory

- [redacted]
- [redacted]
- [redacted]

Study objectives are listed in Table 2-1.

2.2 Study endpoints

Primary

- Incidence rate of Dose Limiting Toxicities (DLT)

Secondary

- Safety will be assessed by monitoring the frequency, duration and severity of adverse events and serious adverse events with a focus on hemorrhagic events, thrombocytopenia, neutropenia, anemia, blood cell component transfusions, or grade 3 or 4 non-hematologic toxicities.
- Plasma INC424 concentration
- Platelets, cytokines and palpable spleen length over time
- Proportion of patients achieving ≥ 50% reduction in palpable spleen length at Week 24 (Study Day 168) relative to Study Day 1

- Change in spleen length as measured by palpation from Study Day 1 to each visit where the variable is measured

Exploratory

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Study endpoints are listed in Table 2-1.

Table 2-1 Objectives and related endpoints

	Objectives	Endpoints	Analysis
Primary	To establish the MSSD of INC424 in patients with MF and baseline PLT count < 100 x 10^9/L and ≥ 75 x 10^9/L (first stratum) and PLT count < 75 x 10^9/L and ≥ 50 x 10^9/L (second stratum)	Incidence rate of Dose Limiting Toxicities (DLT)	Refer to Section 9.4.
Secondary	**Safety:** To characterize the safety of INC424	Safety will be assessed by monitoring the frequency, duration and severity of adverse events and serious adverse events with a focus on hemorrhagic events, thrombocytopenia, neutropenia, anemia, blood cell component transfusions, or grade 3 or 4 non-hematologic toxicities	Refer to Section 9.5.
	Pharmacokinetics: To characterize the pharmacokinetics of INC424 in this patient population	Plasma INC424 concentration	
	Pharmacokinetic-pharmacodynamic relationship: To characterize the pharmacokinetic-pharmacodynamic relationship of this population	Platelets, cytokines and palpable spleen length over time	
	Efficacy: To obtain estimates of efficacy	Proportion of patients achieving ≥ 50% reduction in palpable spleen length at Week 24 (Study Day 168) relative to Study Day 1	
		Change in spleen length as measured by palpation from Study Day 1 to each visit where the variable is measured	
Exploratory	[redacted]	[redacted]	[redacted]

Objectives	Endpoints	Analysis
[redacted]	[redacted]	

3 Investigational plan

3.1 Study design

This is a Phase Ib, open-label, dose-finding study of the JAK inhibitor INC424 tablets administered orally to patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV-MF) or Post-Essential Thrombocythemia-Myelofibrosis (PET-MF) and baseline platelet counts $\geq 50 \times 10^9$/L and $<100 \times 10^9$/L.

The study will consist of 2 periods:

- The core study period [first 168 days of study]
- The extension study period [beyond Week 24 (168 days) to 3 years].

The core study includes patients in one of two phases (Figure 3-1), (a) a dose escalation phase and (b) a safety expansion phase.

In the dose escalation phase, successive cohorts of newly enrolled patients will receive increasing doses of INC424 until the MSSD is determined. The MSSD will be the dose level most closely associated with a posterior DLT probability of between 16% and 33% that does not also have a greater than 25% probability of excessive toxicity. In the safety expansion phase, 20 patients in total (10 patients from each stratum), additional to those treated at the MSSD during dose escalation, will be treated at the respective MSSD for their stratum.

The treatment period for an individual patient is 3 years [except in the UK, which is up to LPFV + 156 weeks]: it will begin on Study Day 1 and will continue until the patient completes the study or is permanently discontinued.

The approximate number of patients planned to be enrolled in the Dose-Determining Set (DDS) for this study is 72, assuming 3 patients are treated at each dose level and 5 dose levels are tested in both strata, and including the additional patients to be enrolled into the 10 mg BID dose which is to be evaluated as a starting dose.

DLT will be defined as the occurrence of any of the following **treatment-related** toxicities occurring through Study Day 28:

- any grade ≥ 2 hemorrhagic event
- any grade thrombocytopenia requiring PLT transfusion
- PLT counts $< 25 \times 10^9$/L*
- grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L)*

- grade ≥ 3 febrile neutropenia*
- grade ≥ 2 total serum bilirubin with coincident direct bilirubin ≥ 0.5 mg/dL
- grade 3 non-hematologic toxicity for ≥ 7 consecutive days
- grade 4 non-hematologic toxicity

*** At the discretion of the Investigator, laboratory values can be confirmed with a second assessment. In this case, only the result of the second assessment will be considered valid and final.**

Adverse events occurring after Study Day 28 will not be considered DLTs, however, they may be considered in further decisions regarding the number of patients to enroll in a given dosing cohort. If a patient is not followed for the 28-day period following Study Day 1 due to discontinuation, for reasons other than DLTs, or if, from Study Day 1 through Study Day 28, a patient misses > 6 consecutive doses of treatment or > 20% of the planned study drug doses, another patient will be enrolled into that dose level and stratum. For toxicities which, by definition, require a time-window for them to be defined as DLTs (grade 3 non-hematologic toxicity for ≥ 7 consecutive days) a subsequent visit(s) and/or laboratory assessment(s) must be scheduled accordingly, in order for this toxicity to qualify as a DLT. A minimum of 9 evaluable patients from each stratum (stratum 1 consists of patients with baseline PLT counts 75-99 $x10^9$/L and stratum 2 consists of patients with baseline PLT counts 50-74 $x10^9$/L) must be treated at the dose declared to be the MSSD.

Enrollment of patients and dose escalation will be performed as described in Section 5.1.2.1, Section 5.1.2.2, Section 5.1.2.3 and Section 5.1.2.4.

Intra-patient escalation during the dose escalation phase of the study will be allowed according to the rules described in the Section 5.1.2.6.

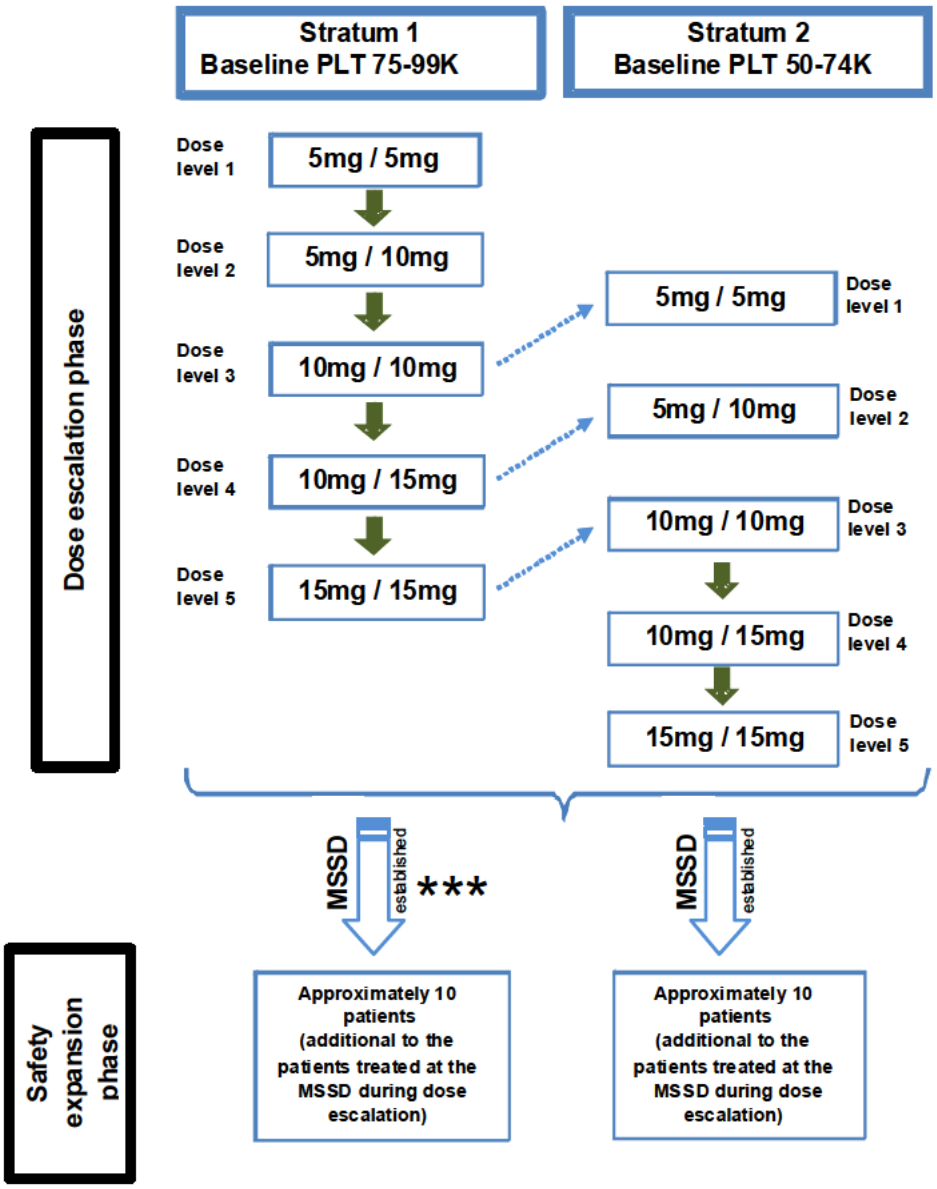
Following determination of the MSSD, a safety expansion phase will be conducted. Patients from both strata can be enrolled simultaneously during the safety expansion phase, allocated to a dose equal to the respective MSSD for their stratum. If the MSSD is the same in both strata, all patients in the safety expansion phase will be treated with the same dose, regardless of the baseline PLT counts.

In the safety expansion phase, the safety and tolerability of the MSSD will be further evaluated with the purpose of establishing that this dose is suitable for use in the low-platelet population of patients with MF. The Bayesian logistic regression model (BLRM) with escalation with overdose control (EWOC) will continue to be updated with data from patients participating in the safety expansion phase.

With the approval of Amendment 4, all new patients enrolled to Stratum 1's safety expansion phase will be given the 10 mg BID dose, instead of the 15 mg BID dose level previously evaluated as the MSSD. This will allow 10 mg BID to be evaluated as the starting dose. Approximately 20 patients will be evaluated at this dose level in Stratum 1, inclusive of the patients already enrolled into this dose during the dose escalation phase, OR the Last Patient's First Visit (LPFV) will occur on 01 September 2017, whichever comes first.

Patients already taking the 15 mg BID dose in Stratum 1's safety expansion phase will continue to take their assigned dose. Stratum 2 will maintain its original enrollment requirement of 10 patients at the MSSD.

Figure 3-1 Study design



Dark arrows: Escalation from a given dose level to he following one, only if both that dose level and the previous one have been deemed safe.

Dotted arrows: Each dose level in Stratum 2 will open to patients only if both that dose level and the following one have been deemed safe in Stratum 1

Note: Once the MSSD criteria have been met for stratum 1, stratum 2 can be independently further escalated, provided that this decision is supported by the BLRM with EWOC. Escala ion for stratum 2 can be continued up to the dose level at which the MSSD criteria have been met for stratum 1, but not higher.

*** As of Amendment 4, new patients enrolled to Stratum 1's safety expansion phase will be given the 10 mg BID dose, instead of the 15 mg BID dose level previously evaluated as the MSSD. Approximately 20 patients will be evaluated at this dose level in Stratum 1, inclusive of the patients already enrolled into this dose during the dose escalation phase, OR the Last Patient's First Visit (LPFV) will occur on 01 September 2017, whichever comes first. Patients already taking the 15 mg BID dose in Stratum 1's safety expansion phase will continue to take their assigned dose.

3.1.1 Investigational treatment, other study treatment, study treatment, supportive treatment

During the study all patients will receive INC424 tablets (see Section 5.1.1). INC424 tablets will be the only investigational drug in this study (Table 3-1).

Table 3-1 Study drugs

Study drugs	
Investigational drug	INC424 tablets (5 mg)

3.1.2 Treatment arms

All patients will receive INC424 tablets. See Figure 3-1 for details regarding dose escalation.

3.1.3 Treatment duration

The study will consist of 2 periods: the initial 24 weeks core treatment period from Study Day 1 to Study Day 168 and the extension treatment period from Study Day 168 (Week 24) until 3 years (Week 156). The core study period consists of a dose escalation phase and a safety expansion phase (Figure 3-1).

[For patients in the United Kingdom only:

After 3 years of study treatment, if the patient continues to benefit in the opinion of the Investigator and does not have access to study drug outside of this clinical trial, the patient may continue on study treatment until LPFV plus 3 years. After LPFV plus 3 years, if the study treatment is not commercially available and reimbursable in the UK, an alternative UK-specific free of charge (FOC) program exists to provide continued access for patients benefitting from the study treatment]

3.1.4 Patient numbering and screening

Each patient is identified in the study by a patient ID number with a maximum length of 9 digits, which is a combination of his/her site ID (the first 4 digits (maximum) of the patient ID) and patient number (the last 5 digits (maximum) of the patient ID) when the patient is first enrolled. The site ID is assigned by the Sponsors to the investigative site. (Novartis Pharmaceuticals and Incyte Corporation are co-sponsors in this study. Novartis is the Sponsor for the European sites only and Incyte is the Sponsor for the US sites only). Upon signing the informed consent form (ICF), the patient number is assigned by the Investigator. In stratum 1, patient numbers will be assigned sequentially per investigative site, beginning with 101. In stratum 2, patient numbers will be assigned sequentially per investigative site, beginning with 201. In the safety expansion phase, patient numbers will be assigned sequentially per investigative site, beginning with 301 in stratum 1 and 401 in stratum 2. Subsequent patients enrolled in each phase of the study will be assigned consecutive patient ID numbers per phase and per site (e.g. the second patient at a site in a specific phase will be assigned patient number 102/202/302/402, the third patient will be assigned patient number 103/203/303/403, etc).

Only the assigned patient ID number should be entered in the field labeled as “patient number” on the EDC data entry screen. Once assigned, the patient number must not be re-

used for any other patient and the patient number for that individual must not be changed, even if the patient is re-screened.

If the patient fails to be started on treatment for any reason, the reason and the patient's demography information should be collected. No other data will be entered into the clinical data base for screen failure patients.

3.1.5 Treatment assignment/randomization

Prior to patient signing of the informed consent form (ICF), the Investigators must contact the Sponsors in order to be informed that the respective cohort and stratum is open to enrollment. The assignment of a patient will be coordinated by the Sponsors in agreement with the Investigators.

3.1.6 Treatment blinding

Not applicable. This is an open label study.

3.2 Rationale for the study design

For a significant population of thrombocytopenic MF patients there are limited data about the safety of INC424 or what might be an appropriate dose. In all studies conducted to date with INC424, baseline PLT count of $\geq$ 100 x10^9/L has been an inclusion criterion. However, thrombocytopenia is a frequent event in MF; as per epidemiology data (Mesa et al 2007), 16.5% of all MF patients are reported to have PLT counts < 100 x10^9/L at diagnosis, while in the intermediate risk-1, -2 or high-risk disease population the incidence of thrombocytopenia is estimated by medical experts to be higher. As noted in Section 1.2.4, thrombocytopenia was established as the DLT of INC424 in MF patients with a MTD of both 25 mg b.i.d. and 100 mg qd. In that study, some patients continued to receive INC424 while their platelet count ranged between 50 and 100 x10^9/L (for details, see Section 3.4.5), but no patients with platelet counts below 100 x10^9/L have initiated INC424 therapy, and therefore the MSSD for patients with low platelets needs to be directly established.

This clinical trial will be a single arm, safety and dose-finding phase Ib study. It will evaluate the safety of INC424 in the low-PLT MF population and will establish the MSSD. Gradually increasing doses of INC424, ranging from 5 mg b.i.d. to 15 mg b.i.d., will be used in the dose escalation part of the study. Initially, only patients with PLT counts 75-99 x10^9/L (first stratum) will allow to be enrolled. Once safety in patients in the first stratum is established at the first two dose cohorts (5 mg b.i.d. and 5 mg q.AM / 10 mg q.PM) the eligible population will be further expanded to patients with PLT counts 50-74 x10^9/L (second stratum).

Following determination of the MSSD, the safety expansion phase will be conducted. In the safety expansion phase, the safety and tolerability of the MSSD will be further evaluated, with the purpose of establishing that this dose is suitable for use in the low-platelet population of patients with MF. Moreover, estimates of efficacy will be obtained.

3.3 Purpose and timing of interim analyses/design adaptations

A Bayesian logistic regression model will be used to assist patients' assignment to treatment dose levels and to guide dose escalation decisions. The dose-finding part of the study requires

data to be reviewed after each cohort is completed in order to determine the best dose for the next cohort of patients.

An interim analysis is planned at the time the MSSD is declared and all patients in the dose escalation phase have completed the core study period. The interim analysis will include primary and secondary endpoints of safety and efficacy. Full PK data will be available at the time of the interim analysis and the results will be reported in a separate PK report.

3.4 Rationale for the dose/regimen selection and treatment duration

3.4.1 Clinical safety and tolerability

3.4.1.1 Healthy volunteers

INC424 has been administered in single or multiple doses to over 200 healthy volunteers. In single dose studies, INC424 has a well established safety profile and has been well tolerated with AEs generally mild in intensity, reversible and of similar incidence following INC424 treatment compared with placebo or with other control treatments. INC424 was examined in a 10-day multiple dose study in a total of 71 healthy volunteers in 6 cohorts who received doses of 50 mg qd, 100 mg qd, 15 mg b.i.d., 25 mg b.i.d. or 50 mg b.i.d. of INC424 or placebo (study [INCB 18424-132]). INC424 was well tolerated in the study, with most Adverse Events reported equally by both INC424-treated and placebo-treated volunteers. Neutropenia, as an AE, 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 SAE. There was a decline in mean ANC and to a lesser extent, mean WBC values with INC424 doses of 15 mg b.i.d. or higher. In general, these declines in ANC or WBC were observed early during the 10-day dosing period with b.i.d. regimens; did not worsen with continued dosing, and returned to baseline levels within 1 to 2 days following the last dose of study drug, suggestive of a neutrophil margination effect. Doses of 25 mg b.i.d. and 100 mg qd were determined to be the maximum tolerated doses in this study. For additional details related to these studies, consult the IB.

A definitive QT study: An Assessment of Heart Rate Corrected QT Intervals in Healthy Subjects Dosed with Single Doses of INC424 Compared with Moxifloxacin ([INCB 18424-138]) 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 results showed little change in the mean heart rate, QRS duration, or QTcF duration indicating a lack of a drug effect. [redacted] A slight increase in PR interval the first hour after dosing was noted, but unlikely to be clinically significant in the opinion of the expert cardiologist. The overall conclusion is that there appears to be no adverse impact on ECG signaling with the administration of INC424.

3.4.1.2 Myelofibrosis patients

INC424, in the context of the [INCB 18424-251] study (refer to Section 1.2.4), has been well tolerated by this aged population with advanced disease. Most adverse events were mild to moderate in severity, considered unrelated to study drug administration and not dose dependent. Related adverse events occurring in at least 8 patients (5%) included in the safety

database through December 31, 2009 were restricted to thrombocytopenia (66 patients, 43%), anemia (45 patients, 29%), weight increased (11 patients, 7%), diarrhea (10 patients, 6.5%) and fatigue (8 patients, 5%). [redacted] Thrombocytopenia represents the DLT in the population of the [INCB 18424-251] study.

For nearly all patients, thrombocytopenia was rapidly reversible and manageable with dose interruption and reduction; low platelet count was the primary reason for study discontinuation for few patients.

Because of the advanced disease present in many of the participants in study [INCB 18424-251], there are a number of SAEs that have been reported that were assessed as unrelated to study drug. Of related SAEs reported in the study to date, the most frequent are those reflecting inhibition of bone marrow function(s) (i.e. thrombocytopenia) and activation of inflammatory cytokines when the inhibitory influence of INC424 is removed due to drug interruption or discontinuation. For more details refer to IB.

3.4.2 Clinical pharmacodynamics

[redacted]

3.4.3 Clinical pharmacokinetics

Absorption: INC424 is a Class 1 molecule under the Biopharmaceutical Classification System, with high permeability, high solubility and rapid dissolution characteristics. In clinical studies, INC424 is rapidly absorbed after oral administration with maximal plasma concentration (C_{max}) achieved approximately 1.5 hours post-dose. Based on a mass balance study in humans, oral absorption of INC424 was $\geq$ 95%. Mean INC424 C_{max} and total exposure (AUC) increased proportionally over a single dose range of 5-200 mg. Administration with a high-fat meal moderately decreased INC424 mean C_{max} by 24% and slightly increased INC424 mean AUC by 4%.

Distribution: At clinically relevant concentrations of INC424, binding to plasma proteins *in vitro* is approximately 97%, mostly to albumin. A whole body autoradiography study in rats has shown that INC424 does not penetrate the blood-brain barrier.

Metabolism: In vitro studies indicate that CYP3A4 is the major enzyme responsible for metabolism of INC424. Parent compound is the predominant entity in circulation in humans. Two major and active metabolites were identified in plasma representing 30% and 14% of parent AUC with 3-5 fold less potent JAK-related pharmacological activity compared to parent drug in a whole blood assay that measures the inhibition of pSTAT3 following IL-6 stimulation. At clinically relevant concentrations, INC424 does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 and is not a potent inducer of

CYP3A4 based on in vitro studies. Nearly 100% of INC424 is metabolized by the liver, while nearly zero metabolism occurs in the kidney. The kidney is an organ of INC424 excretion and does not metabolize INC424

Elimination: Following a single oral dose of 25 mg [^{14}C]-labeled INC424 in healthy adult volunteers, the recovery of the administered radioactivity was 95.53 ± 4.93%, with 73.61 ± 10.18% and 21.92 ± 5.95% in urine and feces, respectively; indicating that urine was the major route of excretion for INC424-related radioactivity. Parent compound was the predominant entity in circulation, representing 57% of total radioactivity. The mean elimination half-life of INC424 is approximately 3 hours.

3.4.3.1 Healthy volunteers

In healthy volunteers INC424 absorption is rapid, mean peak plasma concentrations are achieved 1-2 hours post dose. Single dose exposure (C_{max} and AUC) increased proportionately with dose (range 5 mg to 200 mg). The mean terminal phase elimination half-life was approximately 3 hours and explains minimal accumulation observed upon repeat dosing. A high fat breakfast slowed the absorption (mean T_{max} increased from 1.3 to 2.7 h), and reduced the mean C_{max} by 24% without significant effect on area under the curve, of a 25 mg INC424 tablet.

In healthy volunteers dosed orally with ^{14}C-INC424, unchanged INC424 was the predominant circulating drug-related entity with two major circulating metabolites observed, both of which are mono-oxidation products. 75% of total radioactivity was recovered in urine, while recovery of parent was minimal. The metabolites of INC424 are pharmacologically active with varying degrees of activity on JAK kinases. The two metabolites with the highest exposure as a fraction of the parent, 30% and 14%, exhibit IC_{50} values for inhibition of IL6 stimulated pSTAT3 in human whole blood that is ≥ 3-4 fold higher than the parent (280 nM). This in vitro estimate for INC424 is in good agreement with the IC_{50} (225 nM) estimated ex vivo with data collected in a multiple dose volunteer study.

3.4.3.2 Special population

Elderly: No overall differences in safety, effectiveness, or pharmacokinetics of INC424 were observed between elderly and younger patients.

Renal Insufficiency: Following a single INC424 dose of 25 mg, the pharmacokinetics were similar in patients with various degrees of renal impairment and in those with normal renal function. INC424 is not removed by dialysis. Patients with end stage renal disease on dialysis had prolonged pharmacodynamic activity (inhibition of IL-6 stimulated STAT3 phosphorylation in whole blood). Patients with severe kidney disease (MDRD-eGFR < 30 mL/min/1.73m^2) or on dialysis will be excluded from this study.

Hepatic Insufficiency: Following a single INC424 dose of 25 mg in patients with varying degrees of hepatic impairment (8 patients per group), the pharmacokinetics and pharmacodynamics of INC424 were assessed. There was no rank order correlation between exposure and degree of hepatic impairment assessed by Child-Pugh scores. The mean AUC for INC424 was increased in patients with hepatic impairment by about 88%, 29% and 66% respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. INC424 pharmacodynamic activity (inhibition of IL-6

stimulated STAT3 phosphorylation in whole blood) showed prolonged activity only in patients with severe hepatic impairment. A dose reduction is recommended for patients with hepatic impairment. Given the limited number of patients included in the above mentioned study and the lack of a clear rank order correlation between PK and degree of hepatic impairment, patients with known hepatocellular disease and patients with evidence of encephalopathy will be excluded from this study.

3.4.3.3 Concomitant use of INC424 and CYP3A4 inhibitors and inducers

INC424 is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isozyme. The effects of the potent CYP3A4 inhibitor ketoconazole on the pharmacokinetics (PK) and pharmacodynamics (PD) of INC424 administered as single oral doses shows that with concomitant dosing of ketoconazole, the observed AUC increase is approximately 2-fold, with a similar effect on the PD effect (cytokine-induced STAT3 phosphorylation). Thus, a dose reduction of 50% for INC424 is appropriate for patients who take ketoconazole or other potent CYP3A4 inhibitors as concomitant medication by reducing the twice daily dose regimen to once daily (see Section 5.1.5). A more modest effect on the PK and PD parameters of INC424 was demonstrated with concomitant dosing of the moderate CYP3A4 inhibitor erythromycin. No dose adjustments are necessary when INC424 is co-administered with erythromycin, or by extension, with other moderate or weak inhibitors of CYP3A4, including grapefruit juice. Additional details as to the clinical pharmacology of INC424 may be found in the IB.

[redacted] However, essentially no difference in the PD effect (cytokine-induced STAT3 phosphorylation) was observed with or without rifampin induction. Increased levels of active metabolites were seen with rifampin dosing. These data indicate that the dose of INC424 need not be modified when dosed with CYP3A4 inducers. However, during the study, use of the potent CYP3A4 inducers (rifampin and St. John's Wort) is prohibited. Use of moderate CYP3A4 inducers (e.g., rifabutin, carbamazepine, and phenytoin) is discouraged, and investigators should seek alternatives where possible. No dose adjustment will be used when these moderate CYP3A4 inducers are co-administered with INC424. Any concomitant use of CYP3A4 inducers must be documented.

For rules regarding use of CYP3A4 inhibitors and inducers, see Section 5.1.5, Section 5.1.9, and Section 5.1.10.

3.4.4 Non-clinical data

[redacted]

[redacted]

More detailed information on nonclinical safety evaluations can be found in the IB.

3.4.5 Dose selection

The starting dose in the dose escalation phase of the study will be 5 mg b.i.d. The dose selection was based on the findings of the [INCB 18424-251] study that has established thrombocytopenia as the DLT of INC424 in MF patients, with a MTD of both 25 mg b.i.d. and 100 mg qd. The incidence of grade ≥ 3 thrombocytopenia in this phase I/II trial was 20% at 10 mg b.i.d., 2.9% at 15 mg b.i.d. and 36% at 25 mg b.i.d. Grade 4 thrombocytopenia events occurred with an incidence of 0%, 0% and 11% for patients who initiated dosing at 10 mg b.i.d., 15 mg b.i.d. or 25 mg b.i.d., respectively. Data from that study showed that patients who entered the study with baseline PLT counts 100-150 $x10^9$/L developed grade ≥ 2 thrombocytopenia more frequently (75% vs. 37%, respectively, for the most commonly used doses that will be relevant to this trial, 10 mg and 15 mg b.i.d.) compared with patients with baseline PLT counts > 150 $x10^9$/L. Thrombocytopenia occurred rapidly (Figure 1-1 and Figure 1-2) and resolved with brief drug interruptions and restarts at (usually) lower doses. Analysis of patients who enrolled in the [INCB 18424-251] study with platelet counts < 150 $x10^9$/L and had extended (many weeks) periods of grade 1 or 2 platelet decline was carried out, in order to identify the dose(s) associated with stable platelet counts in the range of 50 $x10^9$/L to 100 $x10^9$/L. Fourteen patients were identified that fit these criteria; 9 of the patients maintained platelet counts between 50 $x10^9$/L and 100 $x10^9$/L while receiving 5 mg b.i.d., 2 patients maintained platelets in this range taking 10 mg b.i.d., one patient was receiving 5 mg q.AM / 10 mg q.PM, one was receiving 5 mg qd and one was receiving 10 mg qd. Importantly, splenomegaly and/or symptom improvements were maintained in 11 of the 14 patients at a level similar to that observed with their initial, higher dose regimen. [redacted]

During the dose escalation phase, the following dose levels are planned to be tested with regards to safety, particularly:

- 5 mg q.AM / 5 mg q.PM
- 5 mg q.AM / 10 mg q.PM
- 10 mg q.AM / 10 mg q.PM
- 10 mg q.AM / 15 mg q.PM, and
- 15 mg q.AM / 15 mg q.PM.

Twice daily schedule is preferred to once daily posology for this study, because the phase II data from [INC18424-251] study demonstrated better efficacy with this schedule. The phase III trials, [INC18424-351] and [INC18424-352], also use twice daily schedules for the same reason.

The highest INC424 dose allowed in the study will be 15 mg b.i.d. Further dose escalation beyond the MSSD, for additional clinical benefit, although will not be tested in this study, may be feasible in selected MF patients presenting with thrombocytopenia and could be explored in another clinical trial.

3.5 Rationale for choice of combination drugs

Not applicable.

3.6 Rationale for choice of comparators drugs

Not applicable.

3.7 Sub-studies

Not applicable.

3.8 Definition of end of the study

The End of the Study (Last Patient Last Visit, LPLV) will occur after all patients in the study have completed their last assessment as per protocol. Patients who are benefiting from study drug may continue study treatment for the duration of 3 years unless one or more withdrawal criteria (Section 6.1.4.1) are met and if the treatment with INC424 is considered the patient's best therapeutic option by the Investigator.

[The above paragraph will read as follows for the United Kingdom only:

The End of the Study (Last Patient Last Visit, LPLV) will occur after all patients in the study have completed their last assessment as per protocol. Patients who are benefiting from study drug may continue study treatment for 3 years if the treatment with INC424 is considered the patient's best therapeutic option by the Investigator.

After 3 years of study treatment, if the patient continues to benefit in the opinion of the Investigator and does not have access to study drug outside of this clinical trial, the patient may continue on study treatment until LPFV plus 3 years. After LPFV plus 3 years, if the study treatment is not commercially available and reimbursable in the UK, an alternative UK-

specific free of charge (FOC) program exists to provide continued access for patients benefitting from the study treatment.]

The last assessment for each patient is the Follow-up Visit that occurs 30 days after the End of Treatment Visit.

The study treatment is commercially available and reimbursable, or is expected to be by the time patients complete the study, in all countries participating in the trial and thus allows patients completing the study to have continued access to the treatment. The exception is the UK, in which a specific alternative exists to provide continued access to treatment.

3.9 Early study termination

The study can be terminated at any time for any reason by the Sponsors. Should this be necessary, each patient who is active in the study should be seen as soon as possible and be treated as described in Section 6.1.4 for a 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 an early termination of the study.

The following procedures will be performed at the final visit:

- Review of concomitant medications and the antineoplastic therapies since discontinuation of the study drug.
- Complete physical examination including measurement of spleen length below the costal margin by palpation, and body weight.
- Vital signs (blood pressure, pulse, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- 12-lead ECG performed in the recumbent position after 5 minutes of rest.
- Blood sampling for serum chemistry and hematology tests.
- Urine pregnancy test for women of childbearing potential only.
- The Eastern Cooperative Oncology Group (ECOG) status will be recorded.
- [redacted]
- Adverse Events will be assessed.

4 Population

The patient population will consist of male or female individuals, aged 18 years or older, who have been diagnosed with PMF, PPV-MF or PET-MF, 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), as defined by the International Working Group, IWG (Cervantes et al 2009)
- exhibit palpable splenomegaly $\geq$ 5 cm below the costal margin and active symptoms
- exhibit PLT counts $< 100 \times 10^9$/L and $\geq 75 \times 10^9$/L for the first stratum of the trial or PLT counts $< 75 \times 10^9$/L and $\geq 50 \times 10^9$/L for the second stratum.

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 for a second course of treatment.

The Investigator or designee must ensure that only patients who meet all the following inclusion and none of the exclusion criteria are offered enrollment in the study. All data for selection criteria must be verifiable in the patient's source documents.

A written Informed Consent Form (ICF) must be obtained before the start of any screening procedure. For screening procedures refer to Section 6.1.1.

4.1 Inclusion criteria

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

1. Patients 18 years of age or older
2. Patients must be diagnosed with PMF, PPV-MF or PET-MF irrespective of [redacted], guided by the criteria outlined in the 2008 World Health Organization (WHO) criteria for PMF (Table 2 in Tefferi and Vardiman, 2008, Appendix 1a), and the proposed criteria for PPV-MF and PET-MF outlined by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) (Table 1 in Barosi et al, 2008, Appendix 1b).
3. Patients with myelofibrosis requiring therapy must be classified at least as intermediate risk level 1 (1 or more prognostic factors). The prognostic factors, defined by the International Working Group (Cervantes et al 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 x10^9/L)
   - circulating blasts ≥ 1%
   - A hemoglobin value < 10 g/dL must be demonstrated during the 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
4. Patients must have palpable spleen of at least 5 cm from the costal margin to the point of greatest splenic protrusion
5. Patients must have active symptoms of MF as demonstrated by one symptom score of at least 5 (0-10 point scale) or two symptom scores of at least 3 (0 to 10 point scale) on the Screening Symptom Form, SSF (Appendix 2)
6. Patients must fulfill all the following criteria at Screening or at Study Day 1:
   - PLT counts < 100 x 10^9/L and ≥ 75 x 10^9/L for the first stratum of the trial or PLT counts < 75 x 10^9/L and ≥ 50 x 10^9/L for the second stratum
   - coagulation parameters as follows: INR and PTT < 1.5 x ULN

7. Patients with ANC > 1 x 10^9/L at Screening
8. Patients with peripheral blood blast count of < 5% at Screening
9. Patients with an ECOG performance status of 0, 1, or 2 at Screening (Appendix 11)
10. Patients must have discontinued all drugs used to treat underlying MF disease no later than 7 days prior to Screening evaluations visit
11. Patients who have not previously received treatment with a *JAK* inhibitor

4.2 Exclusion criteria

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

1. Pregnant or nursing (lactating) women
2. Women of childbearing potential who are unwilling to take appropriate precautions (from Screening through Follow-up) to avoid becoming pregnant
   - Females of non-childbearing potential are defined as women who (a) are ≥ 55 years of age with history of amenorrhea for 1 year with serum FSH levels > 40 mIU/mL, OR (b) are surgically sterile for at least 12 weeks
   - For females of childbearing potential, appropriate precautions (at least two highly effective contraception methods) are those that are at least 99% effective in preventing the occurrence of pregnancy. These methods should be communicated to the patients and their understanding confirmed (Appendix 3)
3. Patients undergoing treatment with hematopoietic growth factor receptor agonists (i.e. erythropoietin (EPO), granulocyte colony stimulating factor (GCSF), romiplostim, eltrombopag) for at least 30 days prior to receiving the first dose of study drug
4. Patients with any history of PLT counts < 45 x 10^9/L within 30 days prior to Screening, except during treatment for a myeloproliferative neoplasm or treatment with cytotoxic therapy for any other reason. Patients who have received PLT transfusion within 14 days prior to Screening evaluations.
5. Any history or predisposition to clinically significant bleeding
6. Any history of platelet dysfunction and/or bleeding diathesis
7. Any regular use of drugs that interferes with coagulation or inhibits PLT function (Appendix 4).
   NOTE: low doses of aspirin ≤ 125 mg/day are allowed.
8. Patients with inadequate liver or renal function as demonstrated by:
   - encephalopathy grade 1 or more, as per West Haven Criteria (Appendix 5)
   - known hepatocellular disease (e.g. active hepatitis or cirrhosis)
   - total bilirubin ≥ 2 x ULN and subsequent determination of direct bilirubin ≥ 2 x ULN
   - alanine aminotransferase (ALT) > 2.5 x ULN
   - MDRD-eGFR < 30 mL/min/1.73m^2 or on dialysis (Appendix 6)
9. Patients with clinically significant bacterial, fungal, parasitic or viral infection which require therapy. Patients with acute bacterial infections requiring antibiotic use should delay screening/enrollment until the course of antibiotic therapy has been completed
10. Patients with known active hepatitis A, B or C at Screening or with known HIV positivity

11. Patients being treated concurrently with a potent systemic inhibitor or a potent systemic inducer of CYP3A4 at the time of Screening (see Appendix 7)
12. Patients with impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral INC424 (e.g., uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection)
13. Patients who currently are candidates for a stem cell transplantation at the time of the screening assessments
14. Patients with an active malignancy over the previous 5 years, except treated cervical intraepithelial neoplasia, basal cell carcinoma of the skin, or squamous cell carcinoma of the skin, with no evidence for recurrence in the past 3 years
15. Patients with currently rapid or paroxysmal atrial fibrillation, currently uncontrolled or unstable angina, recent (approximately 6 months) myocardial infarction or acute coronary syndrome or any clinically significant cardiac disease (NYHA Class III or IV; Appendix 8)
16. Patients under ongoing treatment with another investigational medication or having been treated with an investigational medication within 30 days or 5 half-lives (whichever is longer) prior to enrollment
17. Patients who have had splenic irradiation within 12 months prior to Screening
18. Patients who are unable to comprehend or are unwilling to sign an informed consent form
19. Patients with active alcohol or drug addiction that, in the investigator's expert judgment, would interfere with their ability to comply with the study requirements
20. Patients with any concurrent condition that, in the Investigator's opinion, would jeopardize the safety of the patient or compliance with the protocol
21. Patients who cannot operate electronic diary equipment, or who cannot read the screen or who cannot speak or read and understand the languages provided with the diary (as per e-diary vendor manual)
22. Subject with a life expectancy of less than 6 months.

5 Treatment

5.1 Treating the patient

The Investigator needs to instruct the patient to take the study drug as per protocol. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record eCRF.

5.1.1 Administration

Table 5-1 Treatment and treatment schedule

Study treatment	Pharmaceutical form and route of administration	Dose	Frequency
INC424	Tablets for oral use	Starting dose 5 mg to be increased or decreased (5 mg steps) per Bayesian design (see Section 5.1.2)	b.i.d. (approximately 12 hours apart: morning and night)

Patients will self-administer INC424 tablets as instructed (see Table 5-1 and Section 5.1.2). If the patient forgets to take a dose, 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 will be given a paper treatment-compliance diary and will be asked to complete it on a daily basis. Patients must carry the diary with them at each Study Visit so as the data to be captured by the site investigative staff (Table 6-1 and Table 6-3).

Patients will not take the morning dose of INC424 on the Study Days 1 and 15 for their timed PK assessment (see Table 6-4); study drug will be administered in the clinic in order to obtain post-dose plasma levels of INC424 (Section 6.2.3). On all other days corresponding to Study Visits, patients will take the morning dose of study drugs prior to the visit.

5.1.2 Dosing and treatment schedule

INC424 tablets will be administered b.i.d. (approximately 12 hours apart: morning and night) orally, with at least 240 mL of any liquid, apart from alcohol, without regard to food, in an outpatient setting.

The dosage strength is 5 mg/tablet INC424 phosphate (free base equivalent). Patients will begin dosing on a b.i.d. schedule.

In the dose escalation phase, the starting dose will be 5 mg b.i.d. and the maximum dose will be 15 mg b.i.d., if MSSD is not reached at a lower dose. An adaptive Bayesian logistic regression model guided by escalation with overdose control will be used to allocate patients into each cohort. The dose-escalation cohorts will be: 5 mg q.AM / 5 mg q.PM, 5 mg q.AM / 10 mg q.PM, 10 mg q.AM / 10 mg q.PM, 10 mg q.AM / 15 mg q.PM, and 15 mg q.AM / 15 mg q.PM (see Table 5-2).

Following determination of the MSSD, a safety expansion phase will be conducted. Patients from both strata can be enrolled simultaneously during the safety expansion phase. If the MSSD is the same in both strata, all patients in the safety expansion phase will be treated with the same dose, regardless of the baseline PLT counts (see Section 5.1.3).

5.1.2.1 Starting dose level for cycle 1

INC424 will be dosed on a flat scale of mg/day (b.i.d.) and not individually adjusted by weight or body surface area. In the dose escalation phase of the study, the starting dose, for both strata, will be 5 mg q.AM / 5 mg q.PM. INC424 tablets of 5 mg are available.

5.1.2.2 Dose escalation levels

Table 5-2 Dose levels

Dose levels	
Dose level 1	5 mg q.AM / 5 mg q.PM
Dose level 2	5 mg q.AM / 10 mg q.PM
Dose level 3	10 mg q.AM / 10 mg q.PM
Dose level 4	10 mg q.AM / 15 mg q.PM
Dose level 5	15 mg q.AM / 15 mg q.PM

Doses will be administered according to the dose escalation schedule listed in Table 5-2. Dose escalation will continue until MSSD is reached.

5.1.2.3 Criteria for dose escalation and determination of MSSD

The primary analysis method is an adaptive Bayesian logistic regression model guided by escalation with overdose control (Babb 1998). To make decisions about escalation to the next dose level, the Investigators and the Sponsors study personnel (including the study physician, a safety physician and a statistician) will evaluate the available clinical and laboratory data (of all patients participating in the study, in all dose levels regardless duration), the toxicity information (including adverse events that are not DLTs) and the recommendations from the BLRM at a dose-escalation decision meeting or teleconference (T/C). Regarding thrombocytopenia, not only absolute PLT values, but also the speed at which the PLT counts decline will be taken into account for dose-escalation or dose-modification decisions. PK analysis data will not be a factor considered during this dose escalation decision process. The meetings should be conducted according to Sponsors' Standard Operating Procedures and further details will be provided in the Study Manual. Both Sponsors' study personnel (Novartis Pharmaceuticals and Incyte Corporation) must be in agreement for dose-escalation decisions and/or MSSD declaration. Drug administration at the next dose level may not proceed until the Investigators receive written confirmation from the Sponsors that the results of the previous dose levels were evaluated and it is safe to proceed to a higher dose level.

Criteria for dose escalation are provided in the Section 3.1 and Section 9.4.2. The MSSD will be the dose level most closely associated with a posterior DLT probability of between 16% and 33% that does not also have a greater than 25% probability of excessive toxicity.

In case the MSSD cannot be established due to lack of toxicity at the dose levels tested, the 15 mg b.i.d. dose will be the proposed dose for the patients in the safety expansion phase.

5.1.2.4 Dose escalation

A prior distribution for the model parameters is derived based on experience with INC424 in adult patients in clinical study [INCB 18424-251], which was the dose-finding study in patients with myelofibrosis that preceded the pivotal phase III studies, [INCB 18424-351] and [INCB 18424-352] (see Section 1.2.4). The model will then be updated after each cohort of patients in each stratum with the DLT data from the current study. A detailed description of the methodology can be found in Section 9.4.2.

The first 3 patients enrolled in the study must be enrolled from stratum 1 (patients with baseline PLT counts 75-99 $x10^9$/L). These 3 patients will be enrolled at the first dose level (dose level 1, Table 5-2). At least 3 evaluable patients are needed per dose level to make dose escalation decisions. The previously mentioned (see Section 5.1.2.3) BLRM with EWOC will be updated after all patients in a cohort become evaluable (for the dose-determining analysis set) or discontinue therapy. The dose-determining set (DDS), as defined in Section 9.1.3, consists of all patients from the safety set who either (a) meet the minimum exposure criterion and have sufficient safety evaluations or (b) discontinue due to DLT. Decisions to escalate will be in accordance with satisfying the overdose control criterion based on the results of this modeling, and will be implemented after a joint teleconference or meeting between Investigators and Sponsors, as described in Section 5.1.2.3. As an exception, if the first 2

patients in the cohort experience DLT before the enrollment of the 3rd patient, the model will be re-evaluated before enrollment of any additional patients to the cohort.

Enrollment will begin in stratum 1 at dose level 1. Once at least 6 patients from stratum 1 are confirmed to be in the dose-determining set (DDS) and dose level 3 is allowed for enrolment in stratum 1, then patients from stratum 2 (patients with baseline PLT counts 50-74 $x10^9$/L) may be enrolled at the first dose level. For the subsequent dose levels, patients in stratum 2 cannot be enrolled unless patients from stratum 1 have been allowed to be enrolled at 2 dose levels higher. Once the MSSD criteria have been met for stratum 1, stratum 2 can be independently further escalated, provided that this decision is supported by the BLRM with EWOC. Escalation for stratum 2 can be continued up to the dose level at which the MSSD criteria have been met for stratum 1, but not higher.

Dose escalation levels are listed in the Table 5-2. A minimum of 9 evaluable patients must be treated at the dose declared to be the MSSD, for each stratum.

5.1.2.5 Safety expansion phase

Once the MSSD of INC424 is identified for both strata in the dose escalation phase of this study, additional patients will be enrolled and treated at this dose in order to further evaluate its safety and tolerability and to obtain estimates of efficacy, with the purpose of establishing that this dose is suitable for use in the low-platelet population of patients with MF. Patients from both strata can be enrolled simultaneously during the safety expansion phase. If the MSSD is identical in both strata, all patients in the safety expansion phase will be treated with the same dose. Prior to Amendment 4, twenty patients (10 patients from each stratum), in addition to the patients treated at the MSSD during the dose escalation phase, were to be evaluated during this part of the study. If the MSSD proves not to be well tolerated with further experience and via continuous update of the Bayesian logistic regression model during this safety expansion phase, then a lower dose may be evaluated to twenty additional patients (10 patients from each stratum).

With the approval of Amendment 4, all new patients enrolled to Stratum 1's safety expansion phase will be given the 10 mg BID dose, instead of the 15 mg BID dose level previously evaluated as the MSSD. This will allow 10 mg BID to be evaluated as the starting dose. Approximately 20 patients will be evaluated at this dose level in Stratum 1, inclusive of the patients already enrolled into this dose during the dose escalation phase, OR the Last Patient's First Visit (LPFV) will occur on 01 September 2017, whichever comes first. Patients already taking the 15 mg BID dose in Stratum 1's safety expansion phase will continue to take their assigned dose. Stratum 2 will maintain its original enrollment requirement of 10 patients at the MSSD.

The criteria for continuation of treatment and dose modification guidelines employed during the dose escalation phase will also be followed during safety expansion phase. Dose escalation above the MSSD will not be allowed.

5.1.2.6 Dose cohort modification

Dose level cohorts are listed in Table 5-2. 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) termination of any further escalation of

study drug. Investigators will receive written confirmation from the Sponsors notifying them that enrollment has been increased or decreased, or that no further enrollment will occur.

5.1.2.7 Intra-patient escalation

Intra-patient dose escalation will only be permitted after Study Day 56. During the course of the study, patients can be dose-escalated to the next higher dose level only once every two cycles (each cycle is 28 days), provided that ALL of the following criteria are met:

- inadequate efficacy is seen with the current dose level, as defined by observation of one or both of the following:
  - not achieving at least a 50% reduction in palpable spleen length compared to Study Day 1
  - lack of meaningful improvement in disease symptoms based on the Investigator's expert judgment.
- no treatment-related toxicity has occurred with the current dose level, resulting in treatment reduction or interruption or discontinuation in the previous 56 days.

For the first 24 weeks of treatment for an individual patient, the dose-escalation requirements will be as follows:

- the maximum dose with which the patient is to be treated does not exceed 15 mg b.i.d. and has been evaluated with at least 3 patients for a minimum of 28 days in that stratum, with no more than 1 out of 3 patients experiencing DLT
- the minimum PLT count during the first 24 weeks period is $\geq 50 \times 10^9$/L OR $\geq 75\%$ of the baseline PLT count the current dose level is lower than the MSSD.

For treatment beyond the first 24 weeks, the dose-escalation requirements will be as follows:

- the maximum dose with which the patient is to be treated is the higher of: the MSSD established for that stratum OR 10 mg bid
- the minimum PLT count at the time of the escalation is $\geq 50 \times 10^9$/L AND is $\geq 75\%$ of the baseline PLT count if a patient experienced a PLT count $\leq 50 \times 10^9$/L OR $\leq 75\%$ of the baseline PLT count beyond the first 24 weeks, a dose escalation may be discussed with the sponsor. If a patient experiences a second episode of PLT count $\leq 50 \times 10^9$/L or $\leq 75\%$ of the baseline PLT count (if it is suspected to be drug related), no further dose escalation will be allowed.

The rules for intra-patient escalation described above are also applicable to patients who have undergone one and only one dose reduction. Conversely, dose reduction rules (described in the Section 5.1.3) also apply to patients who undergo dose escalation. Once a patient undergoes a dose reduction due to treatment-related toxicity, the patient may not have a dose increase unless they have been on a stable dose for at least 28 days with no dose interruptions.

Patients who have experienced treatment-related $\geq$ grade 3 toxicity of any nature aside from thrombocytopenia or grade 4 thrombocytopenia may not dose escalate a second time to the dose level at which this toxicity was seen.

For patients who undergo dose escalation, PLT 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

monthly evaluations. Further recommendation can be given during the T/C meetings, on an individual basis.

Consultation with the Sponsors must occur prior to any intra-patient dose escalation.

5.1.2.8 Dose-limiting toxicity (DLT)

Dose-limiting toxicity (DLT) will be defined as the occurrence of any of the **treatment-related** toxicities occurring up to and including Study Day 28, which are listed in Table 5-3, using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

For the purpose of dose-escalation decisions, only DLTs will be necessarily considered and included in the BLRM. However, adverse events, which occur after Study Day 28 and meet all the criteria for the DLT definition apart from the timing of occurrence, will be considered in ultimate decisions of dose escalation and determinations of how many patients should be evaluated at a given dose level. Prior to enrolling patients into a higher dose level, all adverse events will be reviewed for all patients at the current and the previous dose levels.

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

Table 5-3 Criteria for defining dose-limiting toxicities

Toxicity	Any of the following treatment-related criteria (occurring through Study Day 28)
Hematology	PLT counts < 25 x10^9/L*
	grade 4 neutropenia (ANC < 0.5 x10^9/L)*
	grade ≥ 3 febrile neutropenia*
Other AEs	any grade thrombocytopenia requiring PLT transfusion
	any grade ≥ 2 hemorrhagic event
	grade ≥ 2 serum bilirubin with coincident direct bilirubin ≥ 0.5 mg/dL
	grade 3 non-hematologic toxicity for ≥ 7 consecutive days
	grade 4 non-hematologic toxicity

* At the discretion of the Investigator, laboratory values can be confirmed with a second assessment. In this case, only the result of the second assessment will be considered valid and final.

Patients who experience a DLT will have their therapy with INC424 interrupted and will be followed as described in the Table 5-4. After recovery from the toxicity in question, if the Investigator believes that it is in the patient's best interest to resume therapy with INC424, the patient may resume therapy, only after consultation with the Sponsors, according to the guidelines described in the Section 5.1.3 and the Table 5-4.

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
- 2nd episode of grade ≥3 febrile neutropenia
- grade 3 renal toxicity for ≥ 7 consecutive days
- grade 4 renal toxicity

- grade 4 serum bilirubin with direct bilirubin ≥ 0.5 mg/dL
- grade 4 non-hematologic toxicity

If, from Study Day 1 through Study Day 28, a patient misses > 6 consecutive doses of treatment or > 20% of the planned study drug doses, 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 and stratum in order to reach the required number of patients in the cohort.

5.1.2.9 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 6.1.4.

In the case of PLT transfusion that is considered unrelated to the treatment with INC424 (e.g., car accident causing bleeding and subsequent PLT transfusion despite grade ≤ 3 thrombocytopenia), then no measures should be taken, other than those related to the management of the event (Table 5-4). If the event for which the PLT transfusion was given is considered related to the treatment with INC424, then both the PLT toxicity-handling guidelines and the hemorrhagic event-handling guidelines should be taken into account.

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

5.1.2.9.1 Hematologic toxicity

- In the case of grade 4 thrombocytopenia, assessment of PLT count is recommended to be repeated daily, Monday through Friday, until resolution to grade ≤ 3 thrombocytopenia (it is at the Investigator's discretion to perform PLT count assessments during weekends). The subsequent follow-up should be done as described in Section 5.1.4 and in Table 6-2.
- 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. The subsequent follow-up should be done as described in Section 5.1.4 and in Table 6-2 and Table 6-4.

5.1.3 Dose modification and dose delay

All dose modifications should be based on the worst preceding toxicity. Patients may be allowed dose reductions to 5 mg qd (dose level (-1)). Dose reductions more than one level at a time will not be allowed, except for thrombocytopenia, in which case different rules for dose reductions apply (Table 5-4). Note that the maximum allowed doses are quoted in the part of Table 5-4 where guidelines for dose reduction due to thrombocytopenia are provided; lower doses may be used at investigator discretion. It is recommended that patients who are dose reduced for thrombocytopenia have more frequent hematology assessments. PLT 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 monthly evaluations.

Recovery of platelet counts will allow dose increases according to the guidelines in Table 5-5. Note that once a dose is re-escalated, any subsequent declines in platelet count will require that Table 5-4 be used to determine the new lower dose, or dose interruption.

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 he/she must be discontinued from study medication and withdrawn from the study (see Table 5-2 for dose level definitions).

Dose modifications for toxicities occurring during the DLT-definition period (Study Day 1 through Study Day 28), and considered as treatment-related, will **not** be allowed until the toxicity qualifies as a DLT. After a toxicity event has been characterized as a DLT, a patient can resume therapy with a reduced INC424 dose according to the guidelines provided in the Section 5.1.2.7. Dose modification recommendations after Study Day 28 are described in the Table 5-4.

Any dose modifications must be recorded on the Dosage Administration Record eCRF.

5.1.4 Treatment interruption and treatment discontinuation

Patients may continue treatment with INC424 for the duration of the study or until they experience unacceptable toxicity that precludes any further treatment, disease progression, and/or at the discretion of the Investigator. Patients will be discontinued from the study if they withdraw consent, or if the treating physician judges that further therapy with INC424 is no longer in the patient's best interest.

Criteria for interruption and re-initiation of INC424 treatment are summarized in the Table 5-4. A patient must discontinue treatment with INC424 if, after treatment is resumed at a lower dose, the same toxicity recurs with the same or worse severity. If a patient requires a dose delay of > 28 days, then the patient must be discontinued from the study. Patients who discontinue from the study for a treatment-related adverse event or a treatment-related abnormal laboratory value must be followed as described in Section 6.1.4.

Grading of toxicity will be according to CTCAE Version 4.03.

Doses may be restarted and subsequently increased, according to the Table 5-6, provided that platelet counts recover to $\geq 35 \times 10^9$/L and ANC counts recover to $\geq 0.75 \times 10^9$/L and there is no other toxicity that precludes dosing of the patient. Note that once a dose has been restarted, subsequent declines in platelet or ANC count will require that Table 5-4 be used to determine the new lower dose or dose interruption. It is required that patients who have restarted dosing have more frequent hematology assessments. PLT and ANC 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 monthly evaluations (exception: for grade 4 thrombocytopenia or neutropenia events please refer to Section 5.1.2.9.1).

Table 5-4 Criteria for interruption and re-initiation of INC424 treatment – Recommended dose modifications

	Study Day 1 through Study Day 28		Study Day 29 to End of Treatment (EOT)
Worst Toxicity (CTCAE Grade unless otherwise specified)	**Treatment related toxicity**	**Non-treatment related toxicity**	
	Causality of toxicity and relation to the treatment with INC424 is based on the Investigator's expert judgment		
Hematological			
Neutropenia Grade 1 Grade 2 Grade 3 Grade 4	 Continue at same dose level Continue at same dose level Continue at same dose level *Hold dosing	 Continue at same dose level Continue at same dose level Continue at same dose level Hold dosing	 Continue at same dose level Continue at same dose level Continue at same dose level Hold dosing
	* qualifies as a DLT		
	In case of grade 4 neutropenia, follow-up rules according to Section 5.1.2.9.1. For dose restart guidelines, see Table 5-6.		
Grade ≥3 febrile neutropenia (ANC <1.0 x10^9/L, isolated fever ≥38.3°C or sustained fever >38°C for more than 1 hour)	* Hold dosing until resolved to afebrile neutropenia ≤ grade 2, then ↓ 1 dose level** †	Hold dosing until resolved to afebrile neutropenia ≤ grade 2, then continue at same dose level ‡	Hold dosing until resolved to afebrile neutropenia ≤ grade 2, and: if not related to INC424, then continue at same dose level*** if related to INC424, then ↓ 1 dose level***
	* qualifies as a DLT ** Resume therapy according to the rules of Section 5.1.2.7. † If 2nd episode, then discontinue	‡ If 2nd episode, then discontinue	*** If a second episode of grade ≥3 febrile neutropenia occurs within 28 days, whether related or unrelated, the patient must discontinue

	Study Day 1 through Study Day 28		Study Day 29 to End of Treatment (EOT)
Worst Toxicity (CTCAE Grade unless otherwise specified)	**Treatment related toxicity**	**Non-treatment related toxicity**	
	Causality of toxicity and relation to the treatment with INC424 is based on the Investigator's expert judgment		
Hemorrhagic event of any kind			
Grade 1	Continue at same dose level	Continue at same dose level	If not related to INC424, then continue at same dose level If related to INC424, then hold dosing until resolved completely, then continue at same dose level
Grade 2	* Hold dosing until resolved completely, then ↓ 1 dose level	Hold dosing until resolved completely, then continue at same dose level	Hold dosing until resolved completely, and if not related to INC424, then continue at same dose level if related to INC424, then ↓ 1 dose level
Grade 3	** Discontinue	Hold dosing until resolved completely, then continue at same dose level	Hold dosing until resolved completely, and if not related to INC424, then continue at same dose level if related to INC424, then discontinue
Grade 4	** Discontinue	Hold dosing until resolved completely, then ↓ 1 dose level***	Hold dosing until resolved completely, and if not related to INC424, then ↓ 1 dose level if related to INC424, then discontinue
	* qualifies as a DLT. Resume therapy according to the rules of Section 5.1.2.7. ** qualifies as a DLT.	*** the patient has to be substituted	
	In case of a hemorrhagic event of **any** grade the Investigator is advised to perform coagulation tests and albumin assessment		

	Study Day 1 through Study Day 28		Study Day 29 to End of Treatment (EOT)
Worst Toxicity (CTCAE Grade unless otherwise specified)	**Treatment related toxicity**	**Non-treatment related toxicity**	
	Causality of toxicity and relation to the treatment with INC424 is based on the Investigator's expert judgment		
Renal			
Serum Creatinine Grade 1 Grade 2	Continue at same dose level Continue at same dose level	Continue at same dose level Continue at same dose level	Continue at same dose level If related to INC424, then **either** continue at same dose level **or** hold dosing until resolved to ≤ grade 1, then continue at same dose level[†] If not related to INC424, then continue at same dose level
Grade 3	Continue at same dose level, and if duration ≥7 days*, then discontinue	Hold dosing until resolved to ≤ grade 1, then continue at same dose level	If related to INC424**, then **either** continue at same dose level **or** hold dosing until resolved to ≤ grade 1, then continue at same dose level[†]. In any case, if duration ≥7 days, then discontinue. If not related to INC424, then **either** continue at same dose level **or** hold dosing until resolved to ≤ grade 1, then continue at same dose level[†],
Grade 4	* Discontinue	Hold dosing until resolved to ≤ grade 1, then continue at same dose level	If related to INC424, then discontinue If not related to INC424, then hold dosing until resolved to ≤ grade 1, then continue at same dose level
	* qualifies as a DLT		** If a second episode of grade 3 serum creatinine occurs related to INC424, then the patient must discontinue [†] at the discretion of the Investigator

	Study Day 1 through Study Day 28		Study Day 29 to End of Treatment (EOT)
Worst Toxicity (CTCAE Grade unless otherwise specified)	**Treatment related toxicity**	**Non-treatment related toxicity**	
	Causality of toxicity and relation to the treatment with INC424 is based on the Investigator's expert judgment		
Hepatic			
Total bilirubin Grade 1 Grade 2 or 3	Continue at same dose level If Direct Bilirubin < 0.5 mg/dL, then continue at same dose level If Direct Bilirubin ≥ 0.5*, then hold dosing until Direct Bilirubin < 0.5 mg/dL, then ↓ 1 dose level	Continue at same dose level If Direct Bilirubin < 0.5 mg/dL, then continue at same dose level If Direct Bilirubin ≥ 0.5, then hold dosing until Direct Bilirubin < 0.5 mg/dL, then continue at same dose level	Continue at same dose level If Direct Bilirubin < 0.5 mg/dL, then continue at same dose level If Direct Bilirubin ≥ 0.5, then hold dosing until Direct Bilirubin < 0.5 mg/dL, and if not related to INC424, then continue at same dose level if related to INC424, then ↓ 1 dose level
Grade 4	If Direct Bilirubin < 0.5 mg/dL, then continue at same dose level If Direct Bilirubin ≥ 0.5*, then discontinue	If Direct Bilirubin < 0.5 mg/dL, then continue at same dose level If Direct Bilirubin ≥ 0.5, then discontinue**	If Direct Bilirubin < 0.5 mg/dL, then continue at same dose level If Direct Bilirubin ≥ 0.5, then discontinue
	* qualifies as a DLT. Resume therapy according to the rules of Section 5.1.2.7.	** the patient has to be substituted	
	Patients who develop new onset hepatic impairment (Direct Bilirubin ≥ 0.5 mg/dL) must have coagulation tests and albumin assessment.		
Other adverse events			
Grade 1	Continue at same dose level	Continue at same dose level	If related to INC424, then **either** continue at same dose level **or** ↓ 1 dose level[†] If not related to INC424, then continue at same dose level
Grade 2	Continue at same dose level	Continue at same dose level	If related to INC424, then **either** continue at same dose level **or** ↓ 1 dose level[†] If not related to INC424, then continue at same dose level
Grade 3	Continue at same dose level, and: if duration ≥7 days*, then hold dosing until resolved to ≤ grade 1, then ↓ 1 dose level	Hold dosing until resolved to ≤ grade 1, then continue at same dose level	If related to INC424, then ↓ 1 dose level[†] If not related to INC424, then continue at same dose level

<table>
<tr><td></td><td colspan="6">Study Day 1 through Study Day 28</td><td rowspan="2">Study Day 29 to End of Treatment (EOT)</td></tr>
<tr><td rowspan="2">Worst Toxicity (CTCAE Grade unless otherwise specified)</td><td colspan="3">Treatment related toxicity</td><td colspan="3">Non-treatment related toxicity</td></tr>
<tr><td colspan="6">Causality of toxicity and relation to the treatment with INC424 is based on the Investigator’s expert judgment</td></tr>
<tr><td rowspan="2">Grade 4</td><td colspan="3">** Discontinue</td><td colspan="3">Hold dosing until resolved to ≤ grade 1 or baseline grade, then continue at same dose level</td><td>If related to INC424, then discontinue
If not related to INC424, then hold dosing until resolved to ≤ grade 1 or acceptable grade, then continue at same dose level</td></tr>
<tr><td colspan="3">* qualifies as a DLT and resume therapy according to the rules of Section 5.1.2.7.
** qualifies as a DLT</td><td colspan="3"></td><td>† at the discretion of the Investigator</td></tr>
<tr><td></td><td colspan="7">Isolated values of CTCAE grade ≤ 3 alkaline phosphatase values will not require dose modification or interruption</td></tr>
<tr><td colspan="8">Thrombocytopenia (PLT count at time of decline)</td></tr>
<tr><td rowspan="11"></td><td rowspan="11"></td><td colspan="6">Dose at the Time of the Platelet Decline</td></tr>
<tr><td>5 mg qd</td><td>5 mg b.i.d.</td><td>5 mg q.AM / 10 mg q.PM</td><td>10 mg b.i.d.</td><td>10 mg q.AM / 15 mg q.PM</td><td>15 mg b.i.d.</td></tr>
<tr><td colspan="6">New Maximum Dose That Must be Instituted</td></tr>
<tr><td>≥ 75 x10^9/L</td><td>Continue at same dose level</td><td colspan="6">Continue at same dose level</td></tr>
<tr><td>50 - 74 x10^9/L</td><td>Continue at same dose level</td><td colspan="4" rowspan="2">Continue at same dose level</td><td>10 mg b.i.d.†</td><td>10mg b.i.d.†</td></tr>
<tr><td></td><td></td><td colspan="2">Continue at same dose level‡</td></tr>
<tr><td>35 - 49 x10^9/L</td><td>Continue at same dose level</td><td colspan="2">Continue at same dose</td><td>5 mg b.i.d.</td><td>5 mg b.i.d.</td><td>5 mg b.i.d.</td><td>5 mg b.i.d.</td></tr>
<tr><td>25 - 34 x10^9/L</td><td>Continue at same dose level</td><td>5 mg qd</td><td>5 mg qd</td><td>5 mg qd</td><td>5 mg qd</td><td>5 mg qd</td><td>5 mg qd</td></tr>
<tr><td>< 25 x10^9/L</td><td>* Hold dosing

* qualifies as a DLT. If resolved to ≤ grade 2, resume therapy according to the rules of Table 5-6.</td><td>Discontinue</td><td colspan="5">Hold dosing</td></tr>
<tr><td colspan="6">†Patients from stratum 1 ‡Patients from stratum 2</td></tr>
<tr><td colspan="7">In cases of grade 4 thrombocytopenia, follow-up rules according to Section 5.1.2.9.1.
For dose escalation or dose restart guidelines, see Table 5-5 and Table 5-6.</td></tr>
</table>

Table 5-5 Dose escalation guidelines and allowed maximum doses for patients who have previously decreased dosing for thrombocytopenia

Current Platelet Count	Dose re-escalation guidelines (NOTE: maximum doses are given, lower doses may be used at Investigator's discretion)
25 x10^9/L - 34 x10^9/L	Continue at 5 mg qd until platelet counts ≥ 35 x10^9/L
35 x10^9/L - 49 x10^9/L	Continue at 5 mg b.i.d. until platelet counts ≥ 50 x10^9/L
≥ 50 x10^9/L	May increase dose by 5 mg qd each cycle (28 days) provided platelet count remains ≥ 50 x10^9/L, up to the dose where platelet counts first declined and dose reduction occurred

Table 5-6 Dose restart guidelines and allowed maximum doses for patients who have previously interrupted dose for grade 4 thrombocytopenia or grade 4 neutropenia

Current platelet count	Dose restart guidelines (NOTE: maximum doses are given, lower doses may be used at investigator's discretion)
<35 x10^9/L in a patient who is currently holding dose	Must continue to hold
35 - 49 x10^9/L in a patient who is recovering from a dose hold	5 mg qd for 2 weeks, then increase in 5 mg qd increments, no faster than once every cycle (28 days), provided platelet counts ≥ 50 x10^9/L
≥ 50 x10^9/L in a patient who is recovering from a dose hold	5 mg b.i.d. for at least 2 weeks, then may proceed with 5 mg qd dose increases, no more frequently than once every cycle (28 days), and provided platelets remain ≥ 50 x10^9/L, up to the dose where platelet counts first declined < 25 x10^9/L
Current ANC count	**Dose restart guidelines (NOTE: maximum doses are given, lower doses may be used at investigator's discretion)**
<0.75 x10^9/L in a patient who is currently holding dose	Must continue to hold
0.75 – 1.00 x10^9/L in a patient who is recovering from a dose hold	5 mg qd for 2 weeks, then increase in 5 mg qd increments, no faster than once every cycle (28 days), provided ANC counts > 1.00 x10^9/L
> 1.00 x10^9/L in a patient who is recovering from a dose hold	5 mg b.i.d. for at least 2 weeks, then may proceed with 5 mg qd dose increases, no more frequently than once every cycle (28 days), and provided ANC remain > 1.00 x10^9/L, up to a maximum dose of 5 mg qd **BELOW** the dose where ANC counts first declined < 0.50 x10^9/L
NOTE: Whether the dose interruption occurred because of neutropenia, thrombocytopenia or both, when restarting, both the platelet count and ANC must be considered to determine the restart dose, with the lower calculated dose being used. Also, the maximum dose should always be 5 mg qd **BELOW** the dose where platelet counts first declined < 25 x10^9/L or ANC counts first declined < 0.5 x10^9/L.	

5.1.5 Dose reduction of INC424 for concomitant CYP inhibitor usage

INC424 is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isozyme. With concomitant dosing of potent CYP3A4 inhibitors such as systemic ketoconazole clarithromycin, itraconazole, nefazodone and telithromycin (Appendix 7), plasma exposure of INC424 increases approximately 2-fold. Patients under therapy with a potent CYP3A4 inhibitor cannot be enrolled in the study. Use of CYP3A4 inhibitors during the study is strongly discouraged, and investigators should consider alternative therapies wherever possible. However, if the use of a potent CYP3A4

inhibitor is necessary for the sake of patient's safety, then a dose reduction of ~ 50% for INC424 is appropriate. The following dose-reduction rules should be followed:

- If dose is 5 mg qd, treatment with INC424 has to be interrupted
- If dose is 5 mg b.i.d., change dose to 5 mg qd
- If dose is 5 mg q.AM / 10 mg q.PM, change dose to 5 mg qd
- If dose is 10 mg b.i.d., change dose to 10 mg qd
- If dose is 10 mg q.AM / 15 mg q.PM, change dose to 5 mg b.i.d.
- If dose is 15 mg b.i.d., change dose to 15 mg qd

NOTE: once the course of therapy using a CYP3A4 inhibitor has been completed, the patient may resume his/her prior dose level of INC424 beginning the next day.

5.1.6 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.

5.1.7 Rescue medication

Not applicable.

5.1.8 Permitted concomitant therapy

The patient needs to notify the investigative 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 blood transfusions) administered after the patient starts treatment with study drug must be listed on the Concomitant medications/Significant non-drug therapies after start of study drug eCRF.

5.1.9 Permitted concomitant therapy requiring caution and/or action

The following medications have restrictions on use or doses or require changes to the way in which INC424 is administered during the study:

- Systemic corticosteroid doses greater than the equivalent of 10 mg prednisolone per day are not permitted, unless use is part of an INC424-dose tapering strategy (see Section 5.1.6).
- During the study, the concomitant use of potent systemic CYP3A4 **inhibitors** is strongly discouraged. However, when such a concomitant administration of a potent systemic CYP3A4 inhibitor (ketoconazole, clarithromycin, itraconazole, nefazodone and telithromycin, see Appendix 7) is required for subject management, the dose of INC424 must be adjusted as described in Section 5.1.5. Based on the low overall bioavailability of topical ketoconazole, with very low systemic levels seen following topical administration, no dose adjustment of INC424 is needed for use with topical ketoconazole. No dose adjustments are necessary when INC424 is co-administered with erythromycin, or by extension, with other moderate or weak inhibitors of CYP3A4, including grapefruit juice (see Appendix 7).
- During the study, the use of moderate CYP3A4 inducers (e.g., rifabutin, carbamazepine, and phenytoin) is discouraged, and investigators should seek alternatives where possible. No dose adjustment will be used when moderate CYP3A4 inducers are co-administered with INC424. However, any concomitant use of moderate CYP3A4 inducers (e.g., rifabutin, carbamazepine, phenytoin, see Appendix 7) must be documented.
- Granulocyte growth factors 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.

5.1.10 Prohibited concomitant therapy

The following medications are prohibited during the study:

- Any prior or concomitant use of another JAK inhibitor.
- Any investigational medication (other than INC424) that is not approved for any indication. Use of such medications within 30 days or 5 half-lives, whichever is longer, prior to the first dose of study drug and during the study through the Safety Follow-up Visit is prohibited.
- Use of the potent inducers of CYP3A4 (such as rifampin and St John's Wort), is not permitted at any time during participation in the study (see Appendix 7 for a list of CYP3A4 inducers).
- Any regular use of drugs that interfere with coagulation or inhibit PLT function (except low doses aspirin ≤ 125 mg/day which are allowed) and non-steroidal anti-inflammatory drugs (NSAIDs). For a complete list, see Appendix 4.
- Any other medication for myelofibrosis during the treatment period: hydroxyurea, busulfan, interferon, lenalidomide, thalidomide, anagrelide.

5.1.11 Hormonal contraception allowed/excluded

Females of childbearing potential will be requested to use the combination of two highly effective contraception methods that have been determined to be at least 99% effective as indicated in Exclusion Criterion #2 (see Section 4.2 and Appendix 3).

5.2 Study drug(s)

5.2.1 Packaging and labeling

INC424 will be provided in bottles. Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the drug but no information about the patient.

Table 5-7 Packaging and labeling

Study drugs	Packaging	Labeling (and dosing frequency)
INC424	Tablets in bottle	Labels with no reference to dosing

5.2.2 Supply, receipt and storage

INC 424 must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated assistants have access. Upon receipt, the INC424 should be stored according to the instructions specified on the drug labels.

Table 5-8 Supply and storage of study drugs

Study drugs	Supply	Storage
INC424	Centrally supplied by Sponsors	Refer to study drug label

5.2.3 Dispensing and preparation

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

Table 5-9 Dispensing and preparation

Study Drugs	Dispensing	Preparation
INC424	Tablets including instructions for administration are dispensed by study personnel on an outpatient basis. Patients will be provided with adequate supply of study drug for self-administration at home until their next scheduled study visit.	Not applicable

5.2.4 Drug compliance and accountability

5.2.4.1 Drug compliance

Compliance with the INC424 regimen will be calculated by the Sponsors based on the drug accountability documented by the site staff and the review of the paper treatment-compliance diary completed by the patient and will be monitored by the Sponsors/designee (pill counts in accordance with the relevant Standard Operating Procedures). A patient will be considered sufficiently compliant with INC424 treatment if they have taken at least 83.3% of their prescribed dose over the total duration of study drug dosing.

5.2.4.2 Drug accountability

The Investigator or designee 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 at the completion of the study. Patients will be asked to return all unused study drug and packaging on a regular basis, at the end of the study or at the time of study drug discontinuation. Study investigative site will need to keep used and unused study drug for monitor to source verify drug accountability. Patients will also be asked to complete the paper treatment-compliance diary and carry it with them at each Study Visit.

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

5.2.5 Disposal and destruction

The drug supply can be destroyed at the local Sponsors facility, Drug Supply group or third party, as appropriate, after drug accountability. Any destruction of medication has to be approved / initiated by the monitor.

6 Visit schedule and assessments

6.1 Study flow and visit schedule

With the implementation of Amendment 4, Table 6-1, Table 6-2, and Table 6-3 list all of the assessments and indicate with an "X" the visits when they are performed. All data obtained from these assessments must be supported by data in the patient's source document. The tables indicate which data are entered into the database (D) and which data remain in source documents only (S) (column category). Assessments that generate data for database entry and which are recorded on eCRFs are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g., laboratory data) are listed by test name.

Table 6-1 Visit evaluation schedule post amendment 4 - Core study period (from screening to Day 168)

	Category	Reference to assessment types	Screening	Day 1 to Day 28		Day 29 to Day 56		Day 57 to Day 168					For EOT and FU visits-Refer to Table 6-2 and 6-3
					(± 1-day window)	(+ 3 days)	(± 2-days)	(± 3-days window)					
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day			**-21 to -7**	**1**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**168**	
Obtain Informed Consent	D	6.1.1 / 10.3.	Before screening										
Demography	D	6.1.1.3.	X										
Inclusion/exclusion criteria	D	4.1 / 4.2.	X										
[redacted]													
Discuss pregnancy prevention methods	S	5.1.11.	X										
Prior antineoplastic therapy	D	6.1.1.3.	X										
[redacted]													
Relevant medical history/current medical conditions	D	6.1.1.3.	X										
Measurement of spleen by palpation	D	6.2.1 / 6.2.2.1.	X	X	X	X	X	X	X	X	X	X	
Vital signs	D	6.2.2.2.	X	X	X	X	X	X	X	X	X	X	
Height	D	6.2.2.3.	X										
Weight	D	6.2.2.3.	X	X		X		X	X	X	X	X	

	Category	Reference to assessment types	Screening	Day 1 to Day 28		Day 29 to Day 56		Day 57 to Day 168					For EOT and FU visits-Refer to Table 6-2 and 6-3
					(± 1-day window)	(+ 3 days)	(± 2-days)	(± 3-days window)					
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day			**-21 to -7**	**1**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**168**	
Complete physical examination	D	6.2.2.1.	X	X		X		X	X	X	X	X	
Short physical examination	D	6.2.2.1.			X		X						
ECOG performance status	D	6.2.2.4.	X	X		X		X	X	X	X	X	
[redacted]													
ECG	D	6.2.2.7.1.	X	X		X			X			X	
Laboratory Assessments													
Serum chemistry tests	D	6.2.2.5.3 / Appendix 12	X	X	X	X		X	X	X	X	X	
Hematology	D	6.2.2.5.1 / Appendix 12	X	X	X	X	X	X	X	X	X	X	
Coagulation test	D	6.2.2.5.2 / Appendix 12	X	X		X		X		X		X	
Serum Pregnancy Test	D	6.2.2.5.4.	X										
Urine Pregnancy Test	D	6.2.2.5.4.		X		X		X	X	X	X		

	Category	Reference to assessment types	Screening	Day 1 to Day 28		Day 29 to Day 56		Day 57 to Day 168					For EOT and FU visits-Refer to Table 6-2 and 6-3
					(± 1-day window)	(+ 3 days)	(± 2-days)	(± 3-days window)					
Visit no.			**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Study Day			**-21 to -7**	**1**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**168**	
Blood sampling for PK (*not applicable for patients in safety expansion phase*)	D	6.2.3.		X	X	X		X					
[redacted]													
Prior/concomitant medications	D	6.1.1.3 / 5.1.8, 5.1.9, 5.1.10, 5.1.11.	X	X	X	X	X	X	X	X	X	X	
Adverse events	D	7.1.	X	X	X	X	X	X	X	X	X	X	
INC424 morning dose at site	D	6.2.3.2.		X	X								
Drug accountability assessment (Return of INC424 review of paper compliance diary)	D	5.2.4.2.			X	X	X	X	X	X	X	X	
Dispense INC424	D	5.2.3.		X	X	X	X	X	X	X	X	X	

Table 6-2 Visit evaluation schedule post amendment 4 - Extension study period and End of Treatment

	Category	Reference to assessment types	Extension period (± 7-days window)						Extension visits (UK patients only)	End of treatment (Core or Extension) / [UK only: Week 156 and EOT]	End of follow-up (± 3-days window) (Core or Extension)
Visit no.			**11**	**12**	**13**	**14**	**15**	**16, 17, etc**			
Study Week			**Week 36 (Day 252)**	**Week 48 (Day 336)**	**Week 60 (Day 420)**	**Week 72 (Day 504)**	**Week 84 (Day 588)**	**Week 96+ q12 weeks thru Week 144**	**Week 168 + q12 weeks thru LPFV + 156 weeks**	**Last / Week 156**	**30 days after last dose**
[redacted]											
Measurement of spleen by palpation	D	6.2.1 / 6.2.2.1.	X	X	X	X	X	X		X	X
Vital signs	D	6.2.2.2.	X	X	X	X	X	X		X	X
Weight	D	6.2.2.3.	X	X	X	X	X	X		X	X
Complete physical examination	D	6.2.2.1.								X	
Short physical examination	D	6.2.2.1.	X	X	X	X	X	X			X
ECOG performance status	D	6.2.2.4.	X	X	X	X	X	X		X	X
[redacted]											

	Category	Reference to assessment types	Extension period (± 7-days window)						Extension visits (UK patients only)	End of treatment (Core or Extension) / [UK only: Week 156 and EOT]	End of follow-up (± 3-days window) (Core or Extension)
Visit no.			**11**	**12**	**13**	**14**	**15**	**16, 17, etc**			
Study Week			**Week 36 (Day 252)**	**Week 48 (Day 336)**	**Week 60 (Day 420)**	**Week 72 (Day 504)**	**Week 84 (Day 588)**	**Week 96+ q12 weeks thru Week 144**	**Week 168 + q12 weeks thru LPFV + 156 weeks**	**Last / Week 156**	**30 days after last dose**
ECG	D	6.2.2.7.1.								X If before Day 168	
Prior/concomitant medications	D	6.1.1.3 / 5.1.8, 5.1.9, 5.1.10, 5.1.11.	X	X	X	X	X	X	X	X	X
Adverse events	D	7.1.	X	X	X	X	X	X	X	X	X
Drug accountability assessment (Return of INC424 review of paper compliance diary)	D	5.2.4.2.	X	X	X	X	X	X	X	X	
Dispense INC424	D	5.2.3.	X	X	X	X	X	X	X		
Antineoplastic therapies used for MF since discontinuation of INC424	D	6.1.5.									X

Table 6-3 Laboratory assessment schedule post amendment 4 – Extension study period

	Category	Reference to assessment types	Extension period (± 7-days window)	Extension visits (UK patients only)	End of Treatment (Core or Extension) / [UK only: Week 156 and EOT]	Endpoint follow up (+ 3-days window) (Core or Extension)
Visit No.			**Clinic Visits**			
Study Week			**Weeks 36,48, 60, 72, 84, 96, 108, 120, 132 & 144**	**Week 168 + q12 weeks**	**Last Week 156**	**30 days after last dose**
Serum chemistry tests	D	6.2.2.5.3. / ALT, AST, Alkaline phosphatase, Total and Direct Bilirubin, Albumin, Lactate dehydrogenase, Creatinine, BUN, Sodium, Potassium, Glucose, Calcium, Uric acid (Appendix 12)	X	No lab visits required after Week 156	X	X if occurs in Core Phase
Hematology	D	6.2.2.5.1. / Complete Blood Count (CBC) Differential, including reporting of % blasts, Platelets (Appendix 12)	X		X	X
Urine Pregnancy test	D	6.2.2.5.4.	X		X	
[redacted]					[redacted]	

6.1.1 Screening examination

Prospective participants will be scheduled for a Screening visit by site staff. The window for this visit is Day -21 to Day -7. Site staff should inform patients to come to the clinic after an overnight fast of at least 8 hours or since midnight on the day that blood will be drawn for laboratory assessments. Informed consent must be obtained before any study specific procedures are conducted.

A patient who has a laboratory test result(s), apart from an ECG finding that does not satisfy the eligibility criteria may have the test(s) repeated once. These tests may be repeated as soon as the Investigator believes that the retest result is likely to be within the acceptable range to satisfy the entrance criteria, but should be completed within 13 days of the original Screening Visit date. In this case, the patient will not be required to sign another ICF, and the original patient ID number assigned by the Investigator will be used. In the event that the laboratory test(s) cannot be performed within 13 days of the original Screening Visit, or the re-test(s) do not meet the entrance criteria (apart from platelet count, see also Section 6.1.1.1) or the patient's medical condition has changed significantly during the screening period so that inclusion/exclusion criteria are no longer met, the patient is considered a Screen failure, and must be discontinued from the study. If the patient and Investigator choose to re-screen the patient, the patient must sign a new ICF, a new patient ID number will be assigned by the Investigator, and all required Screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only re-Screen once per stratum for the study. Once the number of patients screened and enrolled in the respective dose cohort and stratum is likely to assure target enrollment, the Sponsors may, at its discretion, close the dose cohort and stratum study to further screening. In this case, patients who screen fail will not be permitted to re-Screen.

6.1.1.1 Eligibility screening

Patients must meet all inclusion and exclusion criteria at Screening or at Day 1 in order to be eligible to proceed to the Treatment Phase of the study.

The platelet count value needs to be within the permitted range at Screening OR at Day 1 to qualify the patient for enrolment for the respective stratum. Platelet count re-tests are authorized at Screening within 13 days and at the planned day of first study treatment within 7 days. Therefore any of the 4 platelet count values (at screening, at screening re-test, at the planned day of first study treatment or at its re-test) may qualify the patient in the study. The day at which the treatment will eventually start will be defined as the Study Day 1. If the platelet count value is not within the permitted range neither at Screening nor at Study Day 1 nor at the re-tests, the patient will be considered a screen 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. Only when eligibility has been confirmed will the patient be assigned to a treatment stratum and dose level. Additionally, investigative site staff will enter patient information into the eCRF, and automated queries will be generated for immediate resolution should patient eligibility be in question based on the patient information entered. [redacted]

[redacted]

6.1.1.2 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure. The reason for not being started on treatment will be entered on the Screening Log and each patient's demographic information and date of screening failure will be on the Demography and the screening disposition eCRF. No other data will be entered into the clinical database for patients who are screen failures.

6.1.1.3 Patient demographics and other baseline characteristics

Complete demographic information (age, gender, race, ethnicity, body weight, and height) will be obtained at Screening along with a complete medical (including MF) history, medication history (prior and concomitant), [redacted]. Included will be the usage of any and all drugs used to treat MF. [redacted]
Adverse Events and Eastern Cooperative Oncology Group (ECOG) status will be assessed and recorded and pregnancy prevention methods will be discussed. Spleen size below the left costal margin by palpation, vital signs (blood pressure, pulse, respiratory rate and body temperature), 12-lead electrocardiogram (ECG), and a complete physical examination will also be performed. Clinical laboratory tests (serum chemistry, hematology, and coagulation tests) and serum pregnancy test will also be performed at Screening and recorded in the eCRF.

Patients will be categorized, at the Screening visit or at the Day 1 visit, according to their qualifying PLT counts into one of the following strata: (a) stratum 1 consisting of patients with baseline PLT counts 75-99 $x10^9$/L and (b) stratum 2 consisting of patients with baseline PLT counts 50-74 $x10^9$/L. This categorization will be used to enable patient enrollment at Study Day 1. In the event the PLT count value qualifies the patient for a specific stratum at Screening, but the value on Day 1 qualifies the patient for the other stratum, and that both strata are open for enrolment, the value at the Day 1 visit will determine the choice of the stratum.

6.1.2 Run-in period

Not applicable.

6.1.3 Treatment period

The core study period will consist of 2 phases: (a) the dose escalation phase and (b) the safety expansion phase that will start once the MSSD is determined. For each individual patient, the treatment period will begin on Study Day 1 and continue until Week 156. See Table 6-1, Table 6-2, and Table 6-3 for more details.

With the implementation of Amendment 4, during the core treatment period, from screening until Day 168, on-treatment study visits are scheduled every 2 weeks in the first 8 weeks (Study Days 1, 15, 29, and 43), then every 4 weeks until Day 168 (Study Days 57, 85, 113,

141, and 168). Thereafter, in the extension study period, the on-treatment study visits will be every 12 weeks from Day 168 (on Days 252, 336, 420, 504, 588, etc.) through Week 144 and an EOT visit scheduled for Week 156. There will not be any required laboratory-only visits.

[The above paragraph will read as follows for the United Kingdom only:

For UK patients only, with the implementation of Amendment 4, during the core treatment period, from screening until Day 168, on-treatment study visits are scheduled every 2 weeks in the first 8 weeks (Study Days 1, 15, 29, and 43), then every 4 weeks until Day 168 (Study Days 57, 85, 113, 141, and 168). Thereafter, in the extension study period, the on-treatment study visits will be every 12 weeks from Day 168 (on Days 252, 336, 420, 504, 588, etc.) through Week 156. After Week 156, patients will return to the site every 12 weeks until LPFV plus 156 weeks, when the EOT visit will be performed. There will not be any required laboratory-only visits.]

For all patients, core treatment period visit windows are as follows: Day 15 has a ± 1-day window, Day 29 has a +3 day window, Day 43 has a ± 2-days window, Study Days 57, 85, 113, 141, and 168 have a ± 3-days window. Extension study period visits have a ± 7-day visit window.

Patients should be told to arrive for all Study Visits after an overnight fast of at least 8 hours, with exception for morning medications for any other medical indication e.g. hypertension should be taken with a small amount of water. However Study Visits should still be conducted if the patient does not adhere to fasting requirements and this will not be considered a protocol violation. If, at any time during the study, a patient experiences unexpected signs or symptoms, additional safety evaluations should be conducted at a regular Study Visit or unscheduled visit.

[For United Kingdom patients only:

Since UK patients can continue beyond the 3 year treatment period, study visits will continue to occur every 12 weeks after Week 156. However, for these subsequent visits, ONLY the following summary eCRFs should be completed: Adverse events, Concomitant Medications, Dose Administration Records, Transfusions, and Non-drug Therapies and Procedures.

Laboratory assessments, vital signs, and physical examination findings will not be captured in the eCRF (unless constituting an adverse event), but will be recorded in the source documents at the study center.

At end of treatment and at study discontinuation, all UK patients, including those with visits after Week 156, are required to complete the end of treatment and study evaluation completion assessments. The corresponding eCRFs will need to be completed.]

6.1.4 Discontinuation of Study Treatment/ Study

Patients may voluntarily discontinue from study treatment and from the study for any reason at any time. If a patient decides to discontinue from the study treatment/ study , the investigator should make a reasonable effort (e.g., telephone, e-mail, letter) to understand the primary reason for this decision (or as per local regulation) 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 and discontinuation from the study for a given patient if he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued and study participation ended under the following circumstances:

- Emergence of the following treatment related adverse events or lab abnormalities (see Section 5.1.2.8 and Table 5-4:
  - Grade 3 or 4 hemorrhagic event of any kind
  - Second episode of grade ≥ 3 febrile neutropenia (ANC < 1.0 x 10^9/L, with a single temperature of ≥ 38.3 °C or a sustained temperature of ≥ 38 °C for more than one hour)
  - Grade 3 renal toxicity for ≥ 7 consecutive days
  - Grade 4 renal toxicity
  - Grade 4 serum bilirubin with direct bilirubin ≥ 0.5 mg/dL
  - Grade 4 non-hematologic toxicity
  - Grade 4 serum creatinine related to treatment from Day 1 to Day 28
  - Second episode of grade 3 or 4 serum creatinine from Study Day 29
  - Grade 4 other adverse event
  - Platelet counts reduce < 25 x 10^9/L while taking INC424 at 5mg qd
- Pregnancy
- The following deviations from the prescribed dose regimen:
  - Interruption of study treatment for > 28 days regardless of reason
  - 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) (5 mg qd), which is the lowest acceptable dosing level for this study.
- There is disease progression (see Section 6.2.1). As an exception, if, despite disease progression which is documented by > 40% increase in spleen size and not by leukemic transformation, the Investigator believes that it is in the patient's best interest to continue therapy with INC424 due to symptomatic improvement, the patient may continue therapy, only after consultation with the Sponsors.
- Use of prohibited treatments (refer to Appendix 1) as determined by Novartis
- Patient undergoes splenic irradiation
- Patient undergoes splenectomy. As an exception, patients who participate in the safety expansion phase of the study are allowed to continue in the study, provided that they have fully recovered from the surgery and are discharged from the hospital.
- Death

- Any other protocol deviation that results in a significant risk to the patient's safety
- Patient has completed 3 years of treatment and another treatment option is available
- Patient is non-complaint with the protocol
- Study is terminated by the Sponsor

Patients whose treatment is interrupted or permanently discontinued from the study due to an Adverse Event or abnormal laboratory value must be followed at least once a week for 30 days, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. All patients will be followed for Adverse Events and Serious Adverse Events for 30 days following the last dose of INC424.

Patients who discontinue study treatment and study participation should return for the assessments indicated in Table 6-1, Table 6-2, and Table 6-3 for safety reasons. 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 6.1.6.

6.1.4.1 Replacement policy

Patients withdrawn from the study will not be replaced.

However, if, from Study Day 1 through Study Day 28, a patient misses > 6 consecutive doses of treatment or > 20% of the planned study drug doses, the patient can continue in the study without being evaluable for DLTs. Consequently, another patient has to be enrolled into the same dose level and stratum in order to reach the required number of patients in the cohort.

6.1.5 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 6-1, Table 6-2, and Table 6-3 for a complete list of assessments for the 30 day follow up evaluation.

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

6.1.6 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.

6.1.7 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 should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for this decision (or as per local regulation) 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.

6.2 Assessment types

6.2.1 Efficacy

Efficacy is a secondary endpoint in this study. The primary response assessment will consist of measurement of the spleen length by manual palpation at the end of week 24 (Study Day 168) in comparison to the Study Day 1 measurement. Patients who have a ≥ 50% reduction in spleen size by palpation compared to the initial measurement at Study Day 1 will be considered as responders, otherwise they will be considered non-responders. Spleen length measurements will continue to be measured after Week 24 to evaluate spleen length and percent change from baseline over time. In addition spleen lengths measurements will be conducted at every study visit in order to exclude disease progression, which is a criterion for patient withdrawal (see Table 6-1, Table 6-2, Table 6-3 and Section 6.1.4.1). Disease progression will be documented by > 40% increase in spleen size by palpation compared to the initial measurement at Study Day 1 **or** by disease symptoms progression based on the Investigator's expert judgment **or** by leukemic transformation (as evidenced by bone marrow blast counts of at least 20%, or peripheral blast counts of at least 20% lasting at least 2 weeks).

The edge of the spleen shall be determined by palpation, and measured in centimeters, from the costal margin to the point of greatest splenic protrusion. Investigators will be provided with a soft centimeter ruler so that palpable spleen length is measured in centimeters and not in finger breadths. No imaging studies of any kind will be required for efficacy assessments.

6.2.2 Safety and tolerability

Safety will be monitored by assessing as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.

6.2.2.1 Physical examination, weight, height

A complete physical examination will be performed, as noted in Table 6-1, Table 6-2, and Table 6-3. It will include the examination of general appearance and vital signs (blood pressure [BP], respiratory rate, temperature and pulse), skin, head, eyes, ears, nose, neck (including thyroid), throat, lungs, heart, abdomen (liver, spleen), back, lymph nodes, edema and extremities, vascular and neurological. In addition, the examination will include body systems as indicated by patient symptoms, AEs, prior physical examination, past medical history or other findings as determined by the Investigator. Measurement of spleen size, assessed by palpation and measured in centimeters using a soft ruler, from the costal margin to the point of greatest splenic protrusion, will be performed at every visit. The above described detailed physical examination will be conducted during the Screening Visit, the first day of every treatment cycle, the End of Treatment visit, and the follow up visit (Table 6-1, Table 6-2, and Table 6-3). During the intermediate visits of the cycles 1 and 2, only short physical examinations will be performed, which will include general appearance and vital signs (blood pressure [BP], respiratory rate, temperature and pulse), skin, lungs, heart, abdomen (liver, spleen), edema and extremities, body systems as indicated by patient symptoms, AEs, and measurement of spleen size (Table 6-1, Table 6-2, and Table 6-3).

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 is signed must be recorded on the Adverse Event page of the patient's eCRF.

6.2.2.2 Vital signs

Vital signs (blood pressure, pulse, respiratory rate and body temperature) will be collected according to the Visit Schedule outlined in Table 6-1, Table 6-2, and Table 6-3. 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.

6.2.2.3 Height and weight

Height in centimeters (cm) will be measured only at screening. Body weight in kilograms (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured during the Screening Visit, the first day of every treatment cycle, the End of Treatment visit, and the follow up visit (Table 6-1, Table 6-2, and Table 6-3).

6.2.2.4 Performance status

The performance status will be assessed according to the ECOG performance status scale as noted in Table 6-1, Table 6-2, and Table 6-3. The ECOG performance status is graded on a six point scale (range 0 to 5): 0=Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction); 1=Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work); 2=Symptomatic, < 50% in bed during the day (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=Symptomatic, > 50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours);

4=Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair) and 5=Death.

6.2.2.5 Laboratory evaluations

All laboratory assessments will be performed locally, at the Investigator's site laboratory. For the schedule of the laboratory assessments, see Table 6-1, Table 6-2, and Table 6-3.

6.2.2.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential including reporting of % of blasts, reticulocytes, and platelet count will be measured locally at every visit (see Table 6-1, Table 6-2, and Table 6-3).

6.2.2.5.2 Coagulation test

International Normalized Ratio (INR), Partial Thromboplastin Time (PTT), D-dimer or Fibrinogen Degradation Products (FDP), and fibrinogen will be measured according to Table 6-1, Table 6-2, and Table 6-3. In case of a hemorrhagic event of any grade (CTCAE grade 1 included) the Investigator is advised to perform unscheduled coagulation tests.

6.2.2.5.3 Clinical chemistry

ALT, AST, Alkaline phosphatase, Total and Direct Bilirubin, Albumin, Lactate dehydrogenase, Creatinine, BUN, Sodium, Potassium, Glucose, Calcium, and Uric acid will be measured according to Table 6-1, Table 6-2, and Table 6-3.

6.2.2.5.4 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have a serum beta-hCG test at the screening. Thereafter, the patients will have a urine pregnancy test (Table 6-1, Table 6-2, and Table 6-3). A positive urine pregnancy test requires immediate interruption of study drug until serum beta-hCG is performed and found to be negative. If positive, the patient must be discontinued from the study. All the pregnancy tests will be performed locally.

Women of childbearing potential will be monitored regularly for pregnancy status, either by serum or urine pregnancy tests as described in the study schedule. If local requirements mandate more frequent testing, applicable sites must adhere to these requirements even if scheduled visits are less frequent.

[redacted]

6.2.2.6 Radiological examinations

Not applicable. No imaging studies of any kind will be required for efficacy assessments.

6.2.2.7 Cardiac assessments

6.2.2.7.1 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed:

- at screening
- at Study Days 1, 29, 85, 168
- at the End of Treatment visit if before Day 168

Interpretation of the tracing must be made locally by a physician and documented on the ECG section of the eCRF. Each ECG tracing should be labeled with the study number, patient initials, 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 page of the eCRF. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events page.

6.2.3 Pharmacokinetics

6.2.3.1 Rationale for incorporating pharmacokinetic evaluations

Pharmacokinetic evaluations incorporated in this study will aim to:

1. Compare the low-PLT MF population with the MF population enrolled in the phase I/II [INCB 18424-251] and the phase III [INCB 18424-351] and [INCB 18424-352] studies.
2. Compare safety and efficacy profiles (sensitivity to exposure) of this population to [INCB 18424-251], [INCB 18424-351], and [INCB 18424-352] study populations in order to make dose recommendations for low-platelet MF if there is a clinically significant difference.

6.2.3.2 Pharmacokinetic blood sample collection and handling

Eight blood samples for pharmacokinetic (PK) analyses will be collected from patients over 4 visits in accordance with the study schedule.

Three PK samples will be taken at Study Day 1 visit after completion of screening visit and administration of study drug (Sample #1: 15 minutes to 45 minutes post dose, Sample #2: 1 to 3 hours post dose, and Sample #3: 4-12 hours post dose). Patients will withhold the morning dose of INC424 on the Study Day 15 visit. At the study clinic, Sample #4 will be drawn, just prior to administration of the morning dose of study drug, followed by Sample #5 at 15 minutes to 45 minutes post dose and Sample #6 1 to 3 hours post dose. Sample #7 will be randomly drawn at Study Day 29 visit, and Sample #8 will be randomly drawn at Study Day 57 visit (see Table 6-4).

The exact date and time of the PK blood draws will be recorded along with the dates, times, and mg doses of the last dose of INC424 that preceded the blood draw and any other doses on the day of the blood draw that precede the blood draw. The actual dose regimen from the prior day should also be recorded. Patients that arrive for the Study Day 15 visit having already taken their morning dose should be reminded to come back within the next 2 days for the PK collection without having taken their morning dose. Patients that arrive for Study Day 15 visit, Study Day 29 visit, and Study Day 57 visit and are not sure of the time of their last dose

should be reminded to come back within the next 2 days for PK collection with the time of their last dose. Instructions for sample preparation and shipping will be provided in a laboratory manual.

For each patient, the observed plasma concentration of INC424 will be determined in samples drawn at visits described in the schedule of observations. The time of the prior dose will be recorded on a patient reminder card, and this information will be entered onto the eCRF.

With implementation of amendment 3, PK blood sampling will no longer be required for patients entering into the safety expansion phase.

Table 6-4 Sample collection time windows for population pharmacokinetic assessments

	Study Day 1 Visit 3 samples on the first day of dosing			**Study Day 15 visit 3 samples**			**Study Day 29 visit 1 sample**	**Study Day 57 Visit 1 sample**
Assessment	0.25-0.75 hours post-study drug administration	1-3 hours post-study drug administration	4-12 hours post-study drug administration	Trough: 0.5 hour prior to study drug administration*	0.25-0.75 hours post-study drug administration	1-3 hours post-study drug administration	0-24 hours post-study drug	0-24 hours post-study drug
Sample No	1	2	3	4	5	6	7	8
Plasma sample	X**	X**	X**	X**	X**	X**	X	X

* Sample collected 8-16 hours post-study drug for b.i.d. dose regimen. Study drug administered approximately 30 min after sample collection.

**Plasma samples at these time points are collected on the same day on the single visit specified.

6.2.3.3 Analytical method

The plasma samples will be analyzed for INC424 by a validated LC/MS/MS assay, carried out by the Sponsors' designee. Plasma concentrations of INC424 will be determined following a liquid/liquid extraction procedure using methyl-t butyl ether (MTBE) with $^{13}C_4$-INC424 (INCB028452) as the internal standard. Chromatography will be performed with a Phenomenex Synergi 4µ Polar-RP 80A (30 x 2 mm) column under isocratic conditions and a mobile phase consisting of 55% acetonitrile and 45% 2mM ammonium acetate aqueous solution. LC/MS/MS analysis will be performed using a positive Turbo IonSpray® interface on a Sciex API-3000 and multiple reaction monitoring (MRM). Using 50 µL plasma, this assay produces linear results over a plasma concentration range of 1.0-1000 nM for INC424, corresponding to the lower and upper quantitative limits, respectively.

6.2.4 Other assessments

6.2.4.1 Pharmacodynamics

6.2.4.1.1 Rationale for incorporating pharmacodynamic evaluations

Pharmacodynamic evaluations incorporated in this study will aim to:

- Compare the low-PLT MF population with the MF population enrolled in the phase I/II [INCB 18424-251] and the phase III [INCB 18424-351] and [INCB 18424-352] studies.
- Compare safety and efficacy profiles (sensitivity to exposure) of this study population to [INCB 18424-251], [INCB 18424-351], and [INCB 18424-352] study populations in order to make dose recommendations for low-platelet MF if there is a clinically significant difference.

[redacted]

7 Safety monitoring and reporting

7.1 Adverse events

7.1.1 Definitions and reporting

An Adverse Event for the purposes of this protocol 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 require changes in study medication(s).

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 eCRF. Adverse Event monitoring should be continued for at least 30 days 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 severity of mild, moderate, severe, and life-threatening, **or** grades 1-4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, information about deaths will be collected through a Death form. The occurrence of Adverse Events should be sought by non-directive questioning of the patient during the screening process after signing informed consent and at each visit during the study. Adverse Events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each Adverse Event should be evaluated to determine:

- The severity grade (CTCAE grade 1-4)
- Causality to the Adverse Event (reasonable possibility that the AE is related to the study drug). Since this is an open-label study, the relationship to study drug is only assessed for INC424. For study investigative sites in EU: if the AE is serious, then the causality to INC424 needs to be assessed to comply with requirements according to the EU Clinical Studies Directive.
- Start and end dates, unless unresolved at the follow-up visit
- Action taken with respect to study drug (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)
- Whether it is serious, as per SAE definition provided in Section 7.2.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see Section 7.2.

All Adverse Events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given; patient hospitalized/patient's hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event eCRF.

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 drug, the interventions required to treat it, and the outcome.

Disease progression should not be regarded or reported as an Adverse Event itself unless associated with a separate Adverse Event.

Whenever possible, a diagnosis should be reported instead of underlying signs and symptoms.

7.1.2 Laboratory test abnormalities

7.1.2.1 Definitions and reporting

Abnormal laboratory values or test results that constitute adverse events or underlying conditions should not be reported separately in addition to the respective adverse events or underlying diagnosis.

Additionally, laboratory abnormalities that are considered clinically significant due to induction of clinical signs or symptoms, or requiring concomitant therapy (e.g. any hematologic abnormality that requires transfusion or cytokine treatment) or changes in study medication, should be recorded on the Adverse Events eCRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found.

Laboratory abnormalities, that do not meet the criteria of clinical significance, as judged by the Investigator, 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. Dose modifications described in the Table 5-4 for lab abnormalities should not contribute to designation of a lab parameter abnormality as a SAE.

7.2 Serious adverse events

7.2.1 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 MF, not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - 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
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition
    - Any SAEs that are expected due to MF, including if the SAE is a primary outcome measure, and whether there has been a clear agreement with regulators not to consider these as SAEs, provided the information is collected elsewhere

7.2.2 Reporting

To ensure patient safety, every SAE, **regardless of suspected causality**, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to the Sponsors or designee within 24 hours of learning of its occurrence. Any SAEs experienced after this 30-day period should only be reported to the Sponsors or designee if the Investigator suspects a causal relationship to the study drug. 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. A 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. The investigator must assess and record the relationship of each SAE to the study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the Sponsors' Integrated Medical Safety (IMS) department.

The telephone and telefax number of the contact persons in the local department of Integrated Medical Safety (IMS), 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 person 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 and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure (new occurrence) and is thought to be related to the Sponsors' study drug, a Sponsors' associate may urgently require further information from the investigator for Health Authority reporting. Sponsors 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.

7.2.3 Emergency unblinding of treatment assignment

Not applicable. This will be an open-label study.

7.3 Pregnancies

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the Sponsors 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 Study Pregnancy Form and reported by the Investigator to the Sponsors. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Sponsors' study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.4 Warnings and precautions

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

7.5 Data Monitoring Committee

Not applicable.

7.6 Steering Committee

Not applicable.

8 Data review and management

8.1 Data confidentiality

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

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

In the event that a patient revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) 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.

8.2 Site monitoring

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

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

The Investigator must give the monitor access to all relevant source documents, including electronic documents if that is the source, to confirm their consistency with the eCRF entries. Sponsors monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria and documentation of SAEs. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

8.3 Data collection

The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF) using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained.

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

Automatic validation programs check for data discrepancies in the eCRFs and, by generating appropriate error messages, allow the data to be confirmed or corrected in a timely manner before it is reviewed by the data management (DM) group. Before transfer to the Sponsors (or designated CRO) via a secure network the investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigative site.

8.4 Database management and quality control

Data will be entered into the study database by the designated investigator site staff.

Following data entry into the eCRFs, Sponsors 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 all other discrepancies and missing values and sent to the investigative site via the EDC system.

Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments 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]

All data entry, verification and validation will be performed in accordance with the current standard operating procedures and Validation and Planning (VAP) modules. The VAP will fully document the DM work and data flow within this clinical study. Versions for the computer systems and the coding will be defined in the VAP as will timelines. Data management will be performed under the responsibility of Sponsors BDM department.

The occurrence of any on-going protocol violations will be determined.

At the conclusion of the study, when the database has been declared to be complete and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Biostatistics and Data Management and the Global Head of Clinical development.

9 Statistical methods and data analysis

All data will be analyzed by the Sponsors or a designated CRO. Any data analysis carried out separately by the Investigator should be submitted to the Sponsors in a timely manner before publication or presentation.

The data from all investigative sites who participate in this study will be combined so that an adequate number of patients will be available for analysis.

The data will be summarized with respect to demographic and baseline characteristics, occurrence of dose-limiting toxicities (DLTs), efficacy observations and measurements, safety observations and measurements, and pharmacokinetic/pharmacodynamic measurements.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

All data will be listed unless otherwise specified.

9.1 Analysis sets

In general, data summaries will be presented by dose levels unless otherwise stated. Dose levels may be combined for summary purposes based on the observed outcomes. For example, it may be prudent to summarize according to starting dose received as: lower than MSSD, MSSD, and higher than MSSD. DLT outcomes will be summarized separately by dose level and stratum. Additional key safety information, such as incidence of hematologic adverse events and labs, may be summarized separately by stratum.

9.1.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients who received at least one dose of study medication.

9.1.2 Safety Set

The Safety Set includes all patients who received at least one dose of study medication. Patients will be analyzed according to the study treatment (regimen) they actually received.

A precise definition of "actually received" will be added in the RAP.

9.1.3 Dose-determining Set

The Dose-determining Set (DDS) consists of all patients from the safety set who either (i) meet the minimum exposure criterion and have sufficient safety evaluations as defined below, or (ii) discontinue due to DLT. The patients in the DDS enrolled in the dose-finding part of the study will be the patients used for determination of the MSSD.

A patient is considered to have met the minimum exposure criterion and to have had sufficient safety evaluations if they have not missed > 20% of the planned doses and no more than 6 consecutive doses in the first 28 days, and have completed all required safety evaluations through Study Day 28.

9.1.4 Pharmacokinetic analysis set

The Pharmacokinetic Analysis Set (PAS) consists of all patients with at least one evaluable pre-dose plasma PK sample at any visit. A pre-dose plasma PK sample is defined as evaluable if it is received within 3 hours of the scheduled time (e.g., between 8-16 hours following the previous day dosing).

9.2 Patient demographics/other baseline characteristics

Demographic and other baseline data will be summarized descriptively by dose level for the FAS. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

9.3 Treatments (study drug, concomitant therapies, compliance)

The dose and duration of INC424 will be listed and summarized by dose level using descriptive statistics. Data may be presented by cycle in addition to over the entire study duration. The daily dose will be summarized using descriptive statistics by dose level and will be listed by patient.

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

Compliance to 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. Compliance to study drug, for the period from Study Day 1 to end of treatment, will be summarized by categories of $< 83.3\%$ vs. $\geq 83.3\%$ and will be reported by dose level or combination of dose levels as appropriate.

9.4 Primary objective

The primary objective of the study is to determine the maximum safe starting dose (MSSD) of INC424 given orally, twice-a-day, in a 28-day cycle to patients with myelofibrosis who have baseline platelet counts belonging to 1 of 2 strata: (1) [75 - 100 x 10^9 / L) or (2) [50 - 75 x 10^9 / L).

The corresponding primary analysis method is an adaptive Bayesian logistic regression model guided by escalation with overdose control (EWOC) (Babb et al 1998). A prior distribution for the model parameters is derived based on experience with INC424 in adult patients in clinical study [INCB 18424-251], which was the dose-finding study in patients with myelofibrosis that preceded the pivotal phase III studies [INC424A-351] and [INC424A-352] (see Section 1.2.4). This prior distribution is then updated after each cohort of patients in each stratum with the DLT data from the current study. A detailed description of the used methodology can be found in Section 9.4.2 and Appendix 13.

9.4.1 Variable

Estimation of the MSSD in the dose-escalation part of the study will be based upon the estimation of the probability of DLT for patients in the DDS. This probability is estimated from the model described in Section 9.4.2.

The definition of DLT is provided in Section 5.1.2.7.

9.4.2 Statistical hypothesis, model, and method of analysis

Statistical model

The statistical model for MSSD estimation will be based on a 3-parameter Bayesian logistic regression model. Let $\pi_{(d)}$ be the probability of DLT at total daily dosed (in mg), and let d^* denote a reference dose of INC424. Then the 3-parameter logistic model relating the log-odds for a DLT to the dose and stratum is of the form

$$\text{logit}(\pi_{(d)}) = \log(\alpha) + \beta \log(d/d^*) + \gamma I_{\{\text{pt is in stratum 2}\}},$$

where $\text{logit}(\pi_{(d)}) = \log_e(\pi_{(d)}/(1-\pi_{(d)}))$, $\alpha, \beta > 0$, and $-\infty < \gamma < \infty$. Doses are rescaled as d/d^*, and as a consequence α is equal to the odds of the probability of DLT at d^* for a patient in stratum 1. If a patient is from stratum 2, the indicator $I_{\{\text{pt is in stratum 2}\}}$ takes the value 1, otherwise it takes the value zero. Therefore, γ may be interpreted as the log-odds ratio for the probability of DLT between patients from stratum 2 to patients from stratum 1.

Prior specifications

The derivation of the final prior for usage in this study was a several step process which capitalized on the data observed in the 117 patients treated in the [INCB 18424-251] study at 1 of 4 b.i.d. schedules as described in this section. The general approach was as follows:

Step 1: A Bayesian logistic regression model was applied to the [INCB 18424-251] data using dose and baseline platelet count (as a continuous variable) as covariates, which resulted in posterior estimates for the model parameters, and the effect of the baseline platelet count when treated as a continuous covariate.

Step 2: Using the model from Step 1, the estimated probabilities of DLTs were determined for the patients in stratum 1 of the current study. Since the assumed mean baseline platelet count in stratum 1 is 87 $x10^9$/L (i.e., the midpoint of the range permitted in stratum 1), an extrapolation of the model relative to the [INCB 18424-251] data was required. In addition, an adjustment to the variance estimates was required to account for "between trial heterogeneity". Note that in stratum 1, the indicator applied to γ is zero, so the only model parameters are log (α) and log (β).

Step 3: The adjusted posterior estimates, as described in Step 2 and which are labeled as "Predicted", were assigned 90% relative weight for the final prior. The remaining 10% weight was allocated to an additional "Low toxicity" prior that was developed to ensure the final prior could react reasonably well to data early on that are inconsistent with the prior from Step 2.

Step 4: A minimally informative prior for γ was developed assuming a relatively strong (i.e. conservative) stratum 2 effect.

The final prior for the current study, as well as the resulting DLT prior probability estimates for each stratum, are provided in Table 9-1.

Table 9-1 Final prior for the current study

Prior distributions for the current study: Priors for log (α) and log (β) are normally distributed								
	Means log (α), log (β)			Standard deviations log (α), log (β)		Correlation		Weight
Predicted	-1.010, -0.259			0.876, 0.918		-0.103		0.9
Low toxicity	-1.447, -0.385			1.095, 1.412		-0.065		0.1
Covariate (γ)	log(1.5)			0.354		N/A		N/A
Prior probabilities of under-dosing, targeted, and over-dosing for any DLT								
Total daily dose	**Prior probabilities that P(any DLT) is in interval**			**Mean**	**Standard deviation**	**2.5%**	**50%**	**97.5%**
	[0.0,0.16)	[0.16,0.33)	[0.33,1.00]					
			Stratum 1					
10mg	0.624	0.255	0.121	0.155	0.143	0.001	0.113	0.529
15mg	0.523	0.309	0.168	0.189	0.151	0.006	0.151	0.570
20mg	0.426	0.353	0.221	0.222	0.156	0.018	0.187	0.605
25mg	**0.334**	**0.386**	**0.281**	**0.255**	**0.160**	**0.036**	**0.223**	**0.637**
30mg	**0.249**	**0.395**	**0.355**	**0.289**	**0.165**	**0.053**	**0.261**	**0.670**
			Stratum 2					
10mg	0.502	0.274	0.224	0.207	0.180	0.001	0.159	0.654
15mg	**0.393**	**0.312**	**0.296**	**0.250**	**0.186**	**0.008**	**0.209**	**0.691**
20mg	**0.298**	**0.334**	**0.369**	**0.290**	**0.189**	**0.025**	**0.255**	**0.720**
25mg	**0.215**	**0.339**	**0.446**	**0.329**	**0.191**	**0.048**	**0.300**	**0.748**
30mg	**0.150**	**0.321**	**0.529**	**0.368**	**0.193**	**0.070**	**0.346**	**0.776**
Note: bold values indicate doses not meeting the overdose criterion.								

Further details describing the steps outlined above are provided below.

Step 1

Data from study [INCB 18424-251] were used to derive an informative bivariate normal prior for the model parameters (log(α), log(β)). A 3-parameter Bayesian logistic regression model of the following form was used:

$$\text{logit}(\pi_i) = \log(\alpha_h) + \beta_h \log(d_i/d^*) + \gamma_h(\log(c_i) - c^*),$$

where d_i is the total daily dose and c_i the baseline platelet count of the i-th subject, $\text{logit}(\pi_i) = \log[\pi_i/\{1-\pi_i\}]$, $d^* = 30$mg (total daily dose) is the reference dose of INC424, $c^* = (\log(c_1) + \log(c_2) + \ldots + \log(c_N))/N$ is the arithmetic mean of the logarithm of the baseline platelet counts of the N subjects evaluated in the study, $\alpha_h, \beta_h > 0$ and $-\infty < \gamma_h < \infty$. π_i denotes the probability of a DLT of the i-subject accounted for his/her baseline platelet count. Note also that subscript h was used to denote parameters which were used the fit the data from the study i.e. α_h, β_h and γ_h. This is done in order to distinguish them from the parameters α, β and γ which will be estimated in the current study.

To predict the expected DLT probability π_{pred} at dose d and a certain level of baseline platelet count c_{pred}, the above model was used in the following way:

$$\text{logit}(\pi_{pred,d}) = \log(\alpha_h) + \beta_h \log(d/d^*) + \gamma_h(\log(c_{pred}) - c^*).$$

The exact procedure is then given as follows:

- A non-informative prior for ($\log(\alpha_h)$, $\log(\beta_h)$) and for γ_h was derived in the following way:
  - The median DLT rate at the reference dose (30mg total daily dose) and at c* was assumed 1/3, i.e. mean($\log(\alpha_h)$) = log(1/2)
  - A doubling in dose was assumed to double the odds of DLT, i.e. mean($\log(\beta_h)$) = 0
  - The standard deviations of the two parameters were set to 2, such that the bivariate normal distribution covers approximately 95% of the probability space
  - The correlation was set to 0, assuming independence of $\log(\alpha_h)$ and $\log(\beta_h)$
  - A non-informative prior for γ_h was assumed by specifying a normal prior distribution with mean 0 and standard deviation 2. Note that the 95% interval of this distribution allows for a more than 50-fold increase / decrease in odds depending on the covariate value
- Data from 117 evaluable patients of the [INCB 18424-251] study (see Appendix 13 for the data) were added into the model in order to estimate $\log(\alpha_h)$, $\log(\beta_h)$ and γ_h. The posterior distributions when the data were added into the model can be found in Table 9-2.

Table 9-2 Posterior estimates for BLRM based on study [INCB 18424-251]

Posterior distribution of $\log(\alpha_h)$, $\log(\beta_h)$, data of study [INCB 18424-251], c* = 5.663			
Parameter	Means	Standard deviations	Correlation
$\log(\alpha_h)$, $\log(\beta_h)$	-1.474, -0.324	0.260, 0.822	-0.383
γ_h	-0.383	0.396	N/A

Step 2

The model from Step 1 was used to predict the DLT probability with accompanying 95% credible intervals for the doses to be tested in the study (total daily dose = 10mg, 15mg, 20mg, 25mg and 30mg) for a value of baseline platelet count = 87. This value corresponds approximately to the expected mean baseline platelet count in stratum 1. A multivariate normal distribution for parameters ($\log(\alpha)$, $\log(\beta)$) was derived based on the predicted quantiles such that this distribution fits the predicted dose-response relationship for a baseline platelet count of 87. The predicted quantiles are given in Table 9-3.

The assumption about between-trial heterogeneity was captured in the prior distributions of the standard deviation of ($\log(\alpha)$,$\log(\beta)$), denoted by τ_1 and τ_2. Both τ_1 and τ_2 were assumed to follow a log-normal distribution with mean log(0.5) and standard deviation 0.01, assuming substantial between-trial heterogeneity. The resulting distribution can be found in Table 9-3.

Table 9-3 Predicted probability of DLT quantiles for stratum 1 and distribution of log(alpha), log(beta) after accounting for between trial heterogeneity

Predicted quantiles for doses to be tested in study for c_{pred} = log(87)			
dose (total, daily)	**2.5th quantile**	**Median**	**97.5th quantile**
10mg	0.022	0.122	0.371
15mg	0.045	0.165	0.403
20mg	0.069	0.203	0.431
25mg	0.093	0.237	0.463
30mg	0.114	0.268	0.494
Distribution for log(α), log(β) accounting for between-trial heterogeneity with τ_1, τ_2 ~ lognormal(0.5,0.01^2)			
Parameter	Means	Standard deviations	Correlation
log(α), log(β)	-1.010, -0.259	0.876, 0.918	-0.103

Step 3

In order for the model to allow for the case that the predicted distribution assumes too high toxicity in stratum 1, the prior distribution was set up as a mixture distribution. This mixture consists of the predicted prior distribution and a low-toxicity distribution which assumes the same dose-response relationship for stratum 1 as was seen in study [INCB 18424-251] regardless of baseline platelet count, but accounting for between-trial heterogeneity. The exact procedure to derive the low-toxicity distribution was a follows:

- A non-informative prior for (log(α), log(β)) was derived in the same manner as for the main prior as listed in Step 1 above.
- Data from 117 evaluable patients of the [INCB 18424-251] study (see Appendix 13 for the data) were added into the model in order to estimate log(α), log(β). The posterior distributions when the data were added into the model can be found in Table 9-4.
- The assumption about heterogeneity was captured in the prior distributions of the standard deviation of (log(α), log(β)), denoted by τ_1 and τ_2. Both τ_1 and τ_2 were assumed to follow a log-normal distribution with mean log(0.75) and standard deviation 0.01, assuming substantial to large between-trial heterogeneity. The resulting distribution can be found in Table 9-4.

Table 9-4 Distributions of model parameters and final prior distribution

Posterior distribution of log(α), log(β) using data from study [INCB 18424-251].			
Parameter	**Means**	**Standard deviations**	**Correlation**
log(α), log(β)	-1.443, -0.395	0.258, 0.942	-0.401
Distribution for log(α), log(β) accounting for between-trial heterogeneity with τ_1, τ_2 ~ lognormal(0.75,0.01^2)			
Parameter	**Means**	**Standard deviations**	**Correlation**
log(α), log(β)	-1.447, -0.385	1.095, 1.412	-0.065

Step 4

A prior for the covariate (stratum indicator) parameter, γ, was developed by assuming that patients from the population defined in stratum 2 will have a higher probability of experiencing a DLT at a given dose level than patients from the population defined by stratum 1. Since there are no data available for this estimation, a conservative estimate was developed

based on clinical judgment that set the stratum 2 effect equal to a 1.5 times higher risk in the odds of a DLT at a given dose vs. a patient from Stratum 1. A Normal distribution was assumed with this prior mean and with a variance scaled so that the 97.5th percentile corresponds to a 3 times higher risk on the odds scale, which implies a standard deviation equal to 0.354. This final prior is also given in Table 9-1.

Dose recommendation

After each cohort of patients is completed within a stratum, the posterior distribution for the model parameters will be obtained by simulation. The posterior distributions of the model parameters are used to derive the posterior distributions for $\pi_{(d)}$. The posterior distributions for $\pi_{(d)}$ will be summarized by the following three intervals

- [0,16%) under-dosing
- [16%,33%) targeted toxicity
- [33%,100%] excessive toxicity

Following the principle of dose-escalation with overdose control (EWOC) (Babb et al 2008) and (Neuenschwander et al 2008), after each cohort of patients the recommended dose is the one with the highest posterior probability of DLT in the target interval [16%, 33%) among the doses fulfilling the overdose criteria, namely that there is less than 25% chance that the true rate of DLT falls in the excessive toxicity interval. Note that the dose that maximizes targeted toxicity is the best estimate of the MSSD, but it may not be a safe dose according to the overdose criteria if the amount of data is insufficient. Ideally, if enough data are available, the dose recommended for the next cohort and the best estimate of the MSSD will coincide.

The dose recommended by the adaptive BLRM for each stratum may be regarded as information to be integrated with a clinical assessment of the toxicity profiles observed thus far in determining the next dose to be investigated.

The first 3 patients enrolled in the study must be enrolled from stratum 1. These 3 patients will be enrolled at the first dose level. Once both at least 6 patients from stratum 1 are confirmed to be in the DDS and dose level 3 is allowed for enrolment in stratum 1, then patients from stratum 2 may be enrolled. These 3 patients will be enrolled at the first dose level. Once all patients in a cohort have data sufficient for determination of their inclusion or exclusion from the DDS, their data will be reviewed, together with all previously reviewed data, for dose selection for patients in the next cohort. As an exception, the model will be re-evaluated before enrollment of any additional patients to the cohort if 2 patients in the cohort experience DLT before the enrollment of the 3rd patient.

9.4.3 Handling of missing values/censoring/discontinuations

During the dose-finding part of the trial, one additional patient may be enrolled in each cohort for each patient who does not meet the criteria necessary for inclusion in the dose-determining set. During the dose expansion part of the trial, one additional patient may be enrolled for each patient who does not meet the criteria necessary for inclusion in the safety set. At the time of the study report, patients will have continuing events (e.g., adverse events) summarized using the data cut-off date as the date of completion, with an indication within the listings that the event is continuing.

9.4.4 Supportive analyses

Additional supportive analyses may be conducted if appropriate.

9.5 Secondary objectives

Secondary objectives are listed in Table 2-1.

9.5.1 Efficacy objectives

Spleen measurements by palpation will be obtained with a primary emphasis on the change in measurements from baseline to Week 24. Descriptive statistics will be provided for the spleen length and percent change from baseline over time, including after Week 24. The percentage of patients with at least a 50% reduction in spleen length at any time point as well as at least a 50% reduction in spleen length at Week 24 will be summarized with 95% confidence intervals.

[redacted]

Efficacy endpoints will be summarized for the set of patients from the FAS who have a valid corresponding baseline assessment.

9.5.2 Safety objectives

9.5.2.1 Analysis set and grouping for the analyses

For all safety analyses, the safety set will be used, except for summaries of DLTs, which may be presented for the DDS. All listings will be presented by dose levels and all tables will be presented by dose level or groups of dose levels, as appropriate, based on the number of dose levels used and number of patients treated.

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

- pre-treatment period: from day of patient's informed consent to the day before first dose of study medication
- on-treatment period: from day of first dose of study medication to 30 days after last dose of study medication
- post-treatment period: starting at day 31 after last dose of study medication.

9.5.2.2 Adverse events (AE)

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and post-treatment period are to 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 CTC grades), type of adverse event, relation to the study drug, and by dose level. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event and dose level.

Specific safety event categories (SEC) will be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with the study treatment(s). SECs will be further defined in the study Report and Analysis Plan (RAP). For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

DLTs will be listed and their incidence summarized by primary system organ class, worst grade, type, and dose level. The DDS will be used for these summaries.

9.5.2.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NCI 2009), the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

For 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 and biochemistry laboratory tests:

- frequency table for newly occurring on-treatment grades 3 or 4 (see below for details)
- shift tables using CTCAE grades to compare baseline to the worst on-treatment value
- for laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/(low and high) classification to compare baseline to the worst on-treatment value.
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

Time to onset of grade 3 or higher SECs will be summarized by dose level.

9.5.2.4 Other safety data

ECG

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

Vital signs

Definitions of notably abnormal results will be part of the RAP.

- shift table baseline to worst on-treatment result
- table with descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

Data from other tests (e.g., electrocardiogram or vital signs) will be listed, notable values flagged, and any other information collected will be listed as appropriate.

9.5.2.5 Tolerability

Not applicable.

9.5.3 Resource utilization

Not applicable.

[redacted]

9.5.5 Pharmacokinetics, pharmacodynamics and pharmacokinetics-pharmacodynamics

9.5.5.1 Pharmacokinetic data analysis

The pharmacokinetics of INC424 in this patient population will be estimated by population modeling methodology. INC424 plasma concentrations will be analyzed using NONMEM software. The data from this study may be combined with data from other clinical studies to improve parameter estimation.

9.5.5.2 Pharmacodynamic data analysis

Attempts will be made to characterize the dose/exposure-response relationship read outs of pharmacology, safety and efficacy collected during the study. Relationships between these exposures measures and spleen size, plasma cytokines, platelets, and presence of any dose limiting toxicity will be initially summarized graphically by selected visits of interest, e.g. Study Day 15, Study Day 29, and Study Day 57. If there is evidence of a useful exposure-response relationship, then it will be quantified by an appropriate regression model, e.g., logistic regression.

9.5.5.3 Pharmacokinetic-pharmacodynamic data analysis

The relationship between pharmacokinetic model predicted concentrations/parameters and pharmacologic, safety and efficacy read outs are planned. A longitudinal analysis of platelets (absolute values or change from predose) using predicted pharmacokinetics and baseline platelet value as covariates will be performed to assess platelet change over time.

INC424 plasma concentrations will be analyzed using population PK using NONMEM. PK data may be combined with data from other clinical studies to improve PK parameter estimation. The population PK model will be used to derive estimates of individual steady-state exposure measures using the initial planned dose regimen for the patients in study INC424A2201 (e.g., total mg dose on Day 1, C_{min}, Cmax, and C_{avg} computed over 24 hours).

A longitudinal population PK/PD analysis of platelets will be performed to assess platelets incorporating dose interruptions and dose changes over time if thrombocytopenia is the DLT of most concern and alternative dose regimens or dose adjustment strategies need to be considered for potential use in new clinical studies.

[redacted]

9.7 Interim analysis

A Bayesian logistic regression model will be used to assist patients' assignment to treatment dose levels and to guide dose escalation decisions. The dose-finding part of the study requires data to be reviewed after each cohort is completed in order to determine the best dose for the next cohort of patients.

An interim analysis is planned at the time the MSSD is declared and all patients in the dose escalation phase have completed the core study period. The interim analysis will include primary and secondary endpoints of safety and efficacy. Full PK data will be available at the time of the interim analysis and the results will be reported in a separate PK report.

9.8 Sample size calculation

Cohorts of at least 3 patients per dose level and stratum will be enrolled from the DDS including at least 9 patients at the MSSD level within each stratum from the DDS. Due to the potential for dropouts during the first treatment cycle (e.g. early disease progression), a cohort may be expanded to include additional patient(s). Cohorts may be expanded at any dose level below the MSSD for further elaboration of safety and pharmacokinetic parameters if deemed

appropriate per the CTT. Approximately 21 patients are planned within each stratum in the dose-finding portion of the study assuming 3 patients treated at each dose level and 5 dose levels tested. Once the MSSD is determined, an additional 10 patients will be enrolled per stratum in the safety expansion phase in order to further evaluate the endpoints on patients starting at the MSSD.Based on a review of the interim analysis data, a decision was made to expand the 10 mg BID starting dose for Stratum 1. Following the approval of Amendment 4, new patients enrolled to Stratum 1's safety expansion phase will begin treatment with ruxolitinib at 10 mg BID. In line with the original sample size specification for the MSSD cohorts (i.e. $\geq$ 9 patients for dose escalation phase and 10 patients for safety expansion phase), approximately 20 patients in total will be enrolled, including those already enrolled at the 10 mg BID dose level in Stratum 1.

Patients already taking the 15 mg BID dose in Stratum 1's safety expansion phase will continue to take their assigned dose. Stratum 2 will maintain its original enrollment requirement of 10 patients at the MSSD.

Thus, as of Amendment 4, the approximate number of patients planned to be enrolled in the Dose-Determining Set (DDS) for this study is 72.

10 Ethical considerations and administrative procedures

10.1 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.

10.2 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. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Sponsors before study initiation. 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 Sponsors monitors, auditors, Sponsors Clinical Quality Assurance representatives, designated agents of Sponsors, IRBs/IECs/REBs and regulatory authorities as required.

10.3 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 or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is

capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. 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.

Sponsors 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 Sponsors before submission to the IRB/IEC/REB, and a copy of the approved version must be provided to the Sponsors monitor after IRB/IEC/REB approval.

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

10.4 Discontinuation of the study

Sponsors reserve 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 3.9.

10.5 Publication of study protocol and results

Sponsors assure 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.

10.6 Study documentation, record keeping and retention of documents

The Investigator must ensure that all records pertaining to the conduct of the clinical study, informed consent forms, drug accountability records, source documents, and other study documentation are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

The Investigator must not destroy any records associated with the study without receiving approval from the Sponsors. The Investigator must notify the Sponsors in the event of accidental loss or destruction of any study records. If the Investigator leaves the institution where the study was conducted, the Sponsors must be contacted to arrange alternative record storage options.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document.

All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The Sponsors will retain the original eCRF data and audit trail.

10.7 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 Sponsors. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site.

10.8 Audits and inspections

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

10.9 Financial disclosures

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

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the Investigator contact Sponsors 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 Sponsors and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 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 Sponsors, 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, Sponsors should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

12 References (available upon request)

Babb J, Rogatko A, Zacks S (1998). Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med.; 17 (10):1103-20.

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Appendix 1

Classification and diagnosis of myeloproliferative neoplasms and proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis

Appendix 1a

Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization Criteria and point-of-care diagnostic algorithms (Tefferi and Vardiman, 2008)

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SPOTLIGHT REVIEW

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Classification and diagnosis of myeloproliferative neoplasms: The 2008 World Health Organization criteria and point-of-care diagnostic algorithms

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The 2001 World Health Organization (WHO) treatise on the classification of hematopoietic tumors lists chronic myeloproliferative diseases (CMPDs) as a subdivision of myeloid neoplasms that includes the four classic myeloproliferative disorders (MPDs)—chronic myelogenous leukemia, polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF)—as well as chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES) and 'CMPD, unclassifiable'. In the upcoming 4th edition of the WHO document, due out in 2008, the term 'CMPDs' is replaced by 'myeloproliferative neoplasms (MPNs)', and the MPN category now includes mast cell disease (MCD), in addition to the other subcategories mentioned above. At the same time, however, myeloid neoplasms with molecularly characterized clonal eosinophilia, previously classified under CEL/HES, are now removed from the MPN section and assembled into a new category of their own. The WHO diagnostic criteria for both the classic *BCR–ABL*-negative MPDs (that is PV, ET and PMF) and CEL/HES have also been revised, in the 2008 edition, by incorporating new information on their molecular pathogenesis. The current review highlights these changes and also provides diagnostic algorithms that are tailored to routine clinical practice.
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Keywords: myeloproliferative; classification; diagnosis; WHO; JAK2; V617F

Introduction

When William Dameshek (1900–1969) described the concept of 'myeloproliferative disorders (MPDs)' in 1951,[1] he considered chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF) and erythroleukemia (Di Guglielmo's syndrome) as the original members of the group. Over the years, erythroleukemia has been re-defined as acute erythroid leukemia or its variants,[2] leaving the other four as the classic MPDs. In its 2001 monograph,[3] the World Health Organization (WHO) committee for the classification of myeloid neoplasms assigned the classic MPDs under the broader category of chronic myeloproliferative diseases (CMPDs), which also included chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia/hypereosinophilic syndrome (CEL/HES) and 'CMPD, unclassifiable'.[4] The CMPDs were in turn considered as one of four major categories of chronic myeloid neoplasms, the other three being myelodysplastic syndromes (MDSs), MDS/MPD and mast cell disease (MCD).[3]

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It is now well established that CMPDs share a common stem cell-derived clonal heritage[5] and their phenotypic diversity is attributed to different configurations of abnormal signal transduction, resulting from a spectrum of mutations affecting protein tyrosine kinases or related molecules.[6,7] In principle, therefore, histology-based classification and diagnostic criteria for these disorders can be refined by employing molecular disease markers; for example, the presence of *BCR–ABL* in the context of a chronic myeloid neoplasm is pathognomonic of CML. Accordingly, the 2008 revision of the WHO document on the classification and diagnosis of CMPDs (now referred to as myeloproliferative neoplasms) has incorporated new information on the molecular pathogenesis of both *BCR–ABL*-negative classic MPDs[8–15] and clonal eosinophilic disorders.[16–19] In the current review, we discuss these changes and provide practical diagnostic algorithms that are in line with the formal 2008 WHO criteria.

The 2001 WHO classification system for chronic myeloid neoplasms

As mentioned above, the 2001 WHO classification system recognizes four separate categories of chronic myeloid neoplasms: CMPD, MDS, MDS/MPD and MCD.[3] The CMPD category includes the four classic MPDs (that is CML, PV, ET and PMF) as well as CNL, CEL/HES and 'CMPD, unclassifiable'.[4] The central and shared feature in CMPDs is effective clonal myeloproliferation (that is peripheral blood granulocytosis, thrombocytosis or erythrocytosis) that is devoid of dyserythropoiesis, granulocytic dysplasia or monocytosis. The presence of any one of the latter three features mandated disease assignment to either the MDS or MDS/MPD category.[3]

Myelodysplastic syndromes is considered when myeloid cell dysplasia (one or more lineages) is associated with ineffective hematopoiesis (that is peripheral blood cytopenia).[20] In this regard, although dyserythropoiesis is a common and diagnostic feature in MDS, unilineage dysplasia affecting a non-erythroid cell line can occur in MDS-unclassified (that is neutropenia or thrombocytopenia associated with dysplasia that is restricted to either the granulocyte or megakaryocyte lineage). It should be noted, however, that abnormal megakaryocyte morphology is also seen in CMPD but, in this instance, it is associated with peripheral blood thrombocytosis, granulocytosis or erythrocytosis.

The MDS/MPD category is also characterized by erythroid and/or granulocytic dysplasia.[3] Unlike the case with MDS, however, there is peripheral blood evidence of effective myeloproliferation, often in the form of leukocytosis and/or monocytosis. In other words, patients with MDS/MPD display features that are characteristic of both MDS and CMPD. Included in the MDS/MPD category are chronic myelomonocytic

leukemia (CMML), juvenile myelomonocytic leukemia (JMML), atypical chronic myeloid leukemia (aCML) and 'MDS/MPD, unclassifiable'.[3] It should be noted that the 'M' in aCML stands for 'myeloid' as opposed to 'myelogenous', which is the case in CML.

As for the subcategories of MDS/MPD, diagnoses in both CMML and JMML require the presence of peripheral blood monocytosis ($\geq 1 \times 10^9$ l^{-1}). In aCML, *BCR–ABL*-negative left-shifted granulocytosis is accompanied by granulocytic dysplasia.[21] 'MDS/MPD, unclassifiable' is reserved for the clinical phenotype that displays histological characteristics of both MDS and MPD and yet does not fulfill the diagnostic criteria for CMML, JMML or aCML.[3] 'MDS/MPD, unclassifiable' includes the WHO provisional entity of 'refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T)'; however, the use of the term RARS-T should be restricted to patients who display both dyserythropoiesis (in addition to ringed sideroblasts) and megakaryocytes similar to those in ET, PV or PMF.[22,23]

The 2008 WHO classification of myeloproliferative neoplasms

In the revised 2008 WHO classification system for chronic myeloid neoplasms, the phrase 'disease', in both CMPD and MDS/MPD, is replaced by 'neoplasm'; that is 'CMPD' is now referred to as 'myeloproliferative neoplasm (MPN)' and 'MDS/MPD' as 'myelodysplastic/myeloproliferative neoplasm (MDS/MPN)'. In addition, the MPN category now includes MCD whereas the previous CMPD subcategory of CEL/HES is now reorganized into HES, 'CEL not otherwise categorized (CEL-NOC)' and 'myeloid neoplasms associated with eosinophilia and abnormalities of *PDGFRA*, *PDGFRB* and *FGFR1*' (Table 1).[16–19] The latter group is now assigned a new category of its own whereas both HES and CEL-NOC remain subcategories of MPNs (Table 1). These revisions underscore (i) the neoplastic nature of CMPDs, thus the change from 'disease' to 'neoplasm',[24–33] (ii) the fact that MCD represents another clonal stem cell disease that is akin to other members of MPNs[34–36] and (iii) the presence of molecularly distinct categories among patients with primary eosinophilia.[16–19]

Table 1 The 2008 World Health Organization classification scheme for myeloid neoplasms

1. Acute myeloid leukemia
2. Myelodysplastic syndromes (MDS)
3. Myeloproliferative neoplasms (MPN)
   - 3.1 Chronic myelogenous leukemia
   - 3.2 Polycythemia vera
   - 3.3 Essential thrombocythemia
   - 3.4 Primary myelofibrosis
   - 3.5 Chronic neutrophilic leukemia
   - 3.6 Chronic eosinophilic leukemia, not otherwise categorized
   - 3.7 Hypereosinophilic syndrome
   - 3.8 Mast cell disease
   - 3.9 MPNs, unclassifiable
4. MDS/MPN
   - 4.1 Chronic myelomonocytic leukemia
   - 4.2 Juvenile myelomonocytic leukemia
   - 4.3 Atypical chronic myeloid leukemia
   - 4.4 MDS/MPN, unclassifiable
5. Myeloid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1
   - 5.1 Myeloid neoplasms associated with PDGFRA rearrangement
   - 5.2 Myeloid neoplasms associated with PDGFRB rearrangement
   - 5.3 Myeloid neoplasms associated with FGFR1 rearrangement (8p11 myeloproliferative syndrome)

The 2008 WHO diagnostic criteria for PV, ET and PMF

The first formal attempt in establishing diagnostic criteria for the classic, *BCR–ABL*-negative MPNs focused on PV and was undertaken by the Polycythemia Vera Study Group (PVSG), in 1967.[37] The PVSG subsequently published similar diagnostic criteria for ET.[38] However, the PVSG 'diagnostic' criteria for PV and ET were formulated, primarily, to exclude other causes of erythrocytosis and thrombocytosis, respectively, and establish uniformly applied criteria for entering patients into clinical trials. A major weakness of the PVSG criteria was its suboptimal use of bone marrow histology as a diagnostic tool, which was effectively addressed by the 2001 WHO diagnostic criteria.[4]

The revisions[39] in the 2008 WHO diagnostic criteria for PV, ET and PMF were instigated by the discovery of *JAK2* mutations (for example, *JAK2*V617F, *JAK2* exon 12 mutations) in virtually all patients with PV.[8–13,40–45] Because *JAK2*V617F is myeloid neoplasm-specific and not found in other causes of polycythemia,[46–48] it has lent itself to being a sensitive diagnostic marker for PV.[44] However, in the context of myeloid neoplasms, *JAK2*V617F is not specific for PV and is found in approximately 50% of patients with ET,[49–54] PMF[55,56] or RARS-T,[57–61] and at a lesser frequency in other myeloid neoplasms,[62–70] but not in lymphoid tumors.[46,71–73] Therefore, mutation screening for *JAK2*V617F cannot be used to distinguish one MPN from another, but it does complement histology in the diagnosis of both ET and PMF by excluding the possibility of reactive thrombocytosis or myelofibrosis (Table 2).

At present, laboratory detection of a *JAK2* mutation is not compulsory to make a PV diagnosis since an occasional patient might not display either an exon 12 or an exon 14 *JAK2* mutation in routine clinical samples.[13] Similarly, the absence of *JAK2*V617F has little diagnostic value in ET or PMF since approximately half of the patients are negative for the mutation.[50,55] Furthermore, current assay systems for screening *JAK2* mutations are not standardized and the possibility of both false-positive or false-negative test results should not be ignored, especially in the context of highly sensitive allele-specific assays and low mutant allele burden in the peripheral blood, respectively.[42,74] These issues were taken into account in preparing the revised 2008 WHO document, where MPD-consistent bone marrow histology is listed as a required criterion for the diagnosis of ET, PMF and *JAK2* mutation-negative PV and biologically relevant laboratory and clinical markers are added as minor criteria to solidify a specific diagnosis (Table 2).[39] Finally, the availability of a molecular marker (that is *JAK2*V617F) along with increased utility of bone marrow histology has made it possible to lower the platelet count threshold for ET diagnosis from 600 to 450×10^9l^{-1} and to consider a PV diagnosis at a lower than the WHO-defined hemoglobin target, in the presence of a persistent increase in hemoglobin level in excess of 2 g dl^{-1} from baseline (Table 2).[75,76]

Point-of-care diagnostic algorithms in PV, ET, PMF and primary eosinophilia

An 'increased' hemoglobin or hematocrit does not always equate with a true increase in red cell mass (that is true polycythemia) whereas true PV can sometimes be masked by a normal-appearing hematocrit because of an associated increase

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Table 2 The 2008 World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis

2008 WHO diagnostic criteria

	Polycythemia vera[a]	*Essential thrombocythemia*[a]	*Primary myelofibrosis*[a]
Major criteria	1 Hgb $>18.5\,g\,dl^{-1}$ (men) $>16.5\,g\,dl^{-1}$ (women) or Hgb or Hct >99th percentile of reference range for age, sex or altitude of residence or Hgb $>17\,g\,dl^{-1}$ (men), or $>15\,g\,dl^{-1}$ (women) if associated with a sustained increase of $\geqslant 2\,g\,dl^{-1}$ from baseline that cannot be attributed to correction of iron deficiency or Elevated red cell mass >25% above mean normal predicted value	1 Platelet count $\geqslant 450\times10^{9}\,l^{-1}$	1 Megakaryocyte proliferation and atypia[b] accompanied by either reticulin and/or collagen fibrosis, or In the absence of reticulin fibrosis, the megakaryocyte changes must be accompanied by increased marrow cellularity, granulocytic proliferation and often decreased erythropoiesis (i.e. pre-fibrotic PMF).
	2 Presence of *JAK2*V617F or similar mutation	2 Megakaryocyte proliferation with large and mature morphology. No or little granulocyte or erythroid Proliferation.	2 Not meeting WHO criteria for CML, PV, MDS, or other myeloid neoplasm
		3 Not meeting WHO criteria for CML, PV, PMF, MDS or other myeloid neoplasm	3 Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive marrow fibrosis
		4 Demonstration of *JAK2*V617F or other clonal marker or no evidence of reactive thrombocytosis	
Minor criteria	1 BM trilineage myeloproliferation 2 Subnormal serum Epo level 3 EEC growth		1 Leukoerythroblastosis 2 Increased serum LDH 3 Anemia 4 Palpable splenomegaly

Abbreviations: CML, chronic myelogenous leukemia; EEC, endogenous erythroid colony; Epo, erythropoietin; Hct, hematocrit; Hgb, hemoglobin; LDH, lactate dehydrogenase; MDS, myelodysplastic syndrome; WHO, World Health Organization.
[a]Diagnosis of polycythemia vera (PV) requires meeting either both major criteria and one minor criterion or the first major criterion and 2 minor criteria. Diagnosis of essential thrombocythemia requires meeting all four major criteria. Diagnosis of primary myelofibrosis (PMF) requires meeting all three major criteria and two minor criteria.
[b]Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic and irregularly folded nuclei and dense clustering.

in plasma volume, especially in the presence of marked splenomegaly (that is inapparent PV).[77,78] As such, the distinction among the three *BCR–ABL*-negative classic MPNs (that is PV, ET and PMF) is not always apparent from the hemoglobin or hematocrit reading. In the past, the PVSG advocated the use of red cell mass (RCM) measurement to address the aforementioned shortcomings in the diagnosis of PV.[79] However, such practice was based mostly on a conceptual argument rather than systematic evidence and the 2001 WHO criteria instead emphasized the value of histology in this regard.[80–82]

The association of a *JAK2* mutation with virtually all patients with PV has erased any residual interest in the use of RCM measurement for distinguishing PV from 'secondary' or 'apparent' polycythemia.[13,83,84] Therefore, peripheral blood *JAK2*V617F screening is currently the preferred initial test for evaluating a patient with suspected PV (Figure 1).[85–90] In this regard, we encourage the concomitant determination of serum erythropoietin (Epo) level in order to minimize the consequences of false-positive or false-negative molecular test results (*vide supra*), and also address the infrequent but possible occurrence of *JAK2*V617F-negative PV.[13,74,91–93] In other words, it is highly unlikely that true PV will be both *JAK2*V617F-negative and display normal or elevated serum Epo level.[48] On the other hand, mutation screening for an exon 12 *JAK2* mutation and bone marrow examination should be considered in a *JAK2*V617F-negative patient who displays subnormal serum Epo level (Figure 1).[12,13]

Because *JAK2*V617F also occurs in approximately 50% of patients with either ET or PMF,[51] it is reasonable to include mutation screening in the diagnostic work-up of both thrombocytosis (Figure 2) and bone marrow fibrosis (Figure 3); the presence of the mutation excludes the possibility of reactive myeloproliferation (with the caveat that very low-level positivity might be encountered with use of highly sensitive allele-specific assays)[74] whereas its absence does not exclude an underlying MPN. As such, bone marrow morphological examination is often required for making the diagnosis of both ET and PMF (Figures 2 and 3).[94]

At times, the distinction between PV and *JAK2*V617F-positive ET/PMF might not be clear cut but the therapeutic relevance of being precise in this regard is dubious.[95] We therefore recommend, in such instances, strict adherence to the 2008 WHO criteria for making a working diagnosis and close monitoring of the patient to capture any substantial changes that might warrant revision of diagnosis. Similarly, the possibility of CML mimicking either ET or PMF should always be entertained, especially in the absence of *JAK2*V617F.[96–98] The

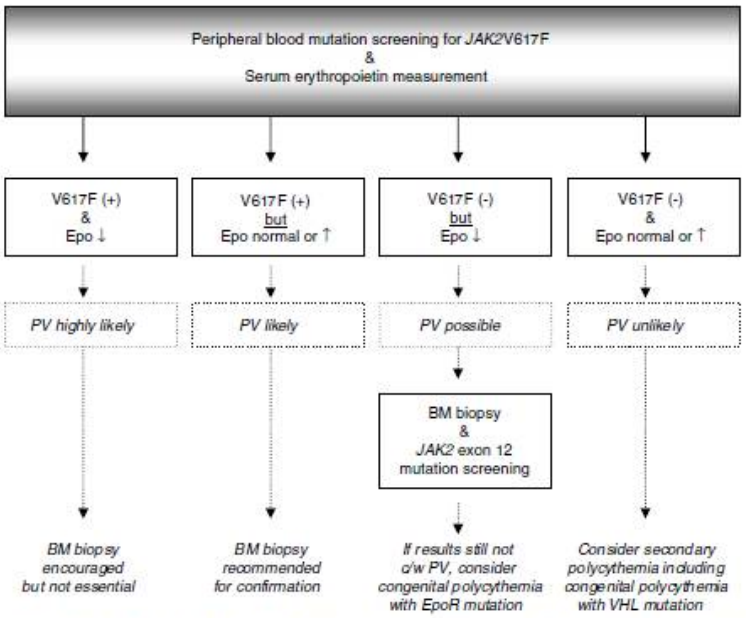

Figure 1 Diagnostic algorithm for suspected polycythemia vera. Key: PV, polycythemia vera; SP, secondary polycythemia; CP, congenital polycythemia; BM, bone marrow; V617F, JAK2V617F; Epo, erythropoietin; EpoR, erythropoietin receptor; VHL, von Hippel–Lindau; c/w, consistent with.

issue is addressed primarily by including cytogenetic studies during bone marrow examination for both PMF and ET and considering fluorescent *in situ* hybridization (FISH) for *BCR–ABL* in the absence of the Ph chromosome but the presence of dwarf bone marrow megakaryocytes (Figures 2 and 3).

Diagnosis in the non-classic MPNs (CNL, HES, CEL-NOC, MCD and 'MPN, unclassifiable'), in general, requires the absence of *BCR–ABL*, dyserythropoiesis, granulocyte dysplasia or monocytosis ($\geqslant 1 \times 10^9 l^{-1}$). CNL is considered in the presence of $\geqslant 25 \times 10^9 l^{-1}$ leukocytes in the peripheral blood accompanied by >80% segmented neutrophils or bands, <10% immature granulocytes and <1% myeloblasts (<5% blasts in the bone marrow).[99] When MCD is suspected, one should consider bone marrow examination with tryptase stain, bone marrow mast cell flow cytometry to look for phenotypically abnormal mast cells (that is CD25-positive), and if available, mutation screening for *KIT*D816V; a working diagnosis can be made in the presence of bone marrow aggregates of morphologically abnormal mast cells or, when histology is equivocal, the presence of either *KIT*D816V or phenotypically abnormal mast cells.[100] 'MPN, unclassifiable' is considered when an MPN clinical phenotype does not meet diagnostic criteria for either the classic or the other non-classic MPNs.[3]

Comprehensive and accurate evaluation of primary eosinophilia requires bone marrow examination with tryptase stain, T-cell clonal studies and immunophenotype, cytogenetic studies and molecular studies to detect *FIP1L1-PDGFRA*.[101] These studies should enable one to distinguish between 'molecularly-characterized myeloid neoplasms associated with eosinophilia', CEL-NOC, and HES (Figure 4). The former category includes *PDGFRA*, *PDGFRB* and *FGFR1* rearranged myeloid neoplasms associated with eosinophilia.[16–19] In the absence of these molecular markers, CEL-NOC or HES is considered; diagnosis in both requires the presence of $\geqslant 1.5 \times 10^9 l^{-1}$ PB eosinophil count, exclusion of secondary eosinophilia, exclusion of other acute or chronic myeloid neoplasm, and no evidence for phenotypically abnormal and/or clonal T lymphocytes.[102] In addition, diagnosis of HES requires absence of both cytogenetic abnormality, and >2% peripheral blasts or >5% bone marrow blasts (Figure 4).[102]

The future: towards genetic classification and diagnosis of myeloid neoplasms

The prospect of genetic classification and diagnosis in myeloid neoplasms started with the 1960 discovery of the Philadelphia (Ph) chromosome in CML.[103] Since then, the Ph chromosome has been molecularly characterized as *BCR–ABL*[104] and additional pathogenetically relevant mutations have been described in both other classic and non-classic MPNs: *JAK2*V617F in PV, ET and PMF;[8,9,11,105] *JAK2* exon 12 mutations in PV;[12,13,15] *MPL*W515L/K in ET or PMF;[41–43] *PDGFRA*, *PDGFRB* or *FGFR1* rearrangements in molecularly characterized myeloid neoplasms associated with eosinophilia;[16,18,19] *KIT*D816V and other *KIT* mutations in MCD;[106] and RAS pathway mutations, including *RAS*, *PTPN11* or *NF1*, in JMML.[107–109] Such discoveries in the molecular pathogenesis

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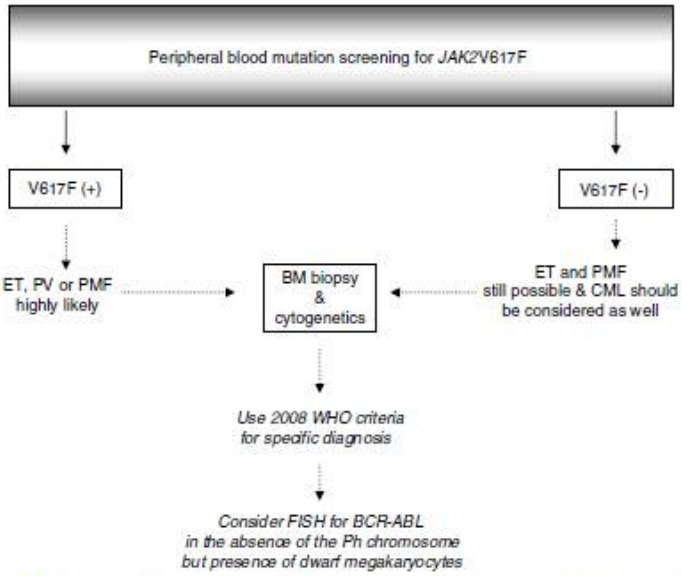

Figure 2 Diagnostic algorithm for suspected essential thrombocythemia. Key: PV, polycythemia vera; ET, essential thrombocythemia; PMF, primary myelofibrosis; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; WHO, World Health Organization; RT, reactive thrombocytosis; FISH, fluorescent *in situ* hybridization; Ph, Philadelphia; BM, bone marrow; V617F, JAK2V617F.

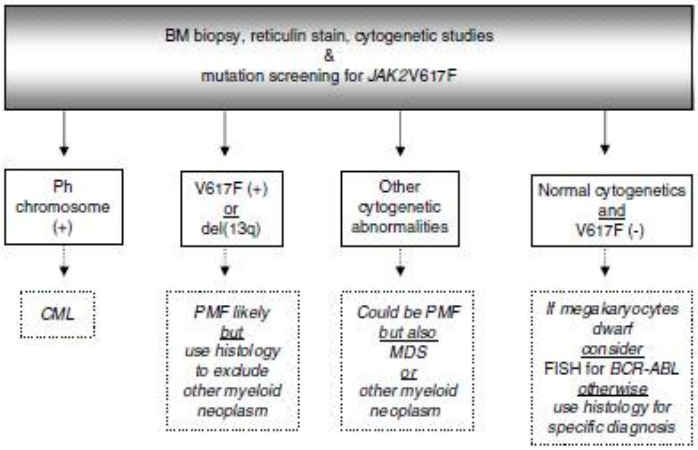

Figure 3 Diagnostic algorithm for suspected primary myelofibrosis. Key: PMF, primary myelofibrosis; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; FISH, fluorescent *in situ* hybridization; Ph, Philadelphia; BM, bone marrow; V617F, JAK2V617F.

of myeloid neoplasms will ultimately lead to a predominantly genetic classification system with disease-specific molecular markers that are relevant to both diagnosis and treatment.[110] For example, mutation screening for *FIP1L1-PDGFRA* (detected by FISH or reverse transcriptase-polymerase chain reaction), *PDGFRB*-rearrangement (detected by karyotype or FISH) or *FGFR1* translocation (detected by karyotype) is now essential for accurate disease classification and choosing appropriate therapy in a patient with primary eosinophilia, thus validating the CML–*BCR–ABL* paradigm.[101] We expect more of such changes in future revisions of the WHO monograph as anatomic pathology continues to be enhanced by molecular information and the

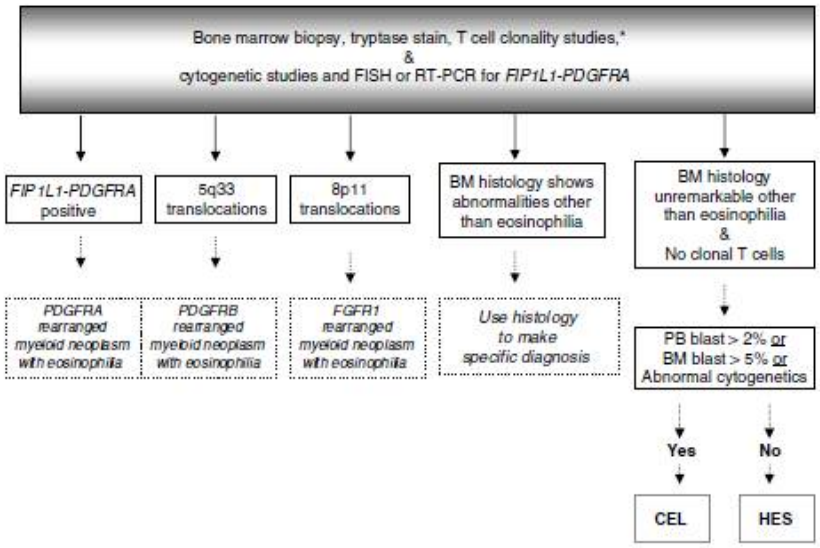

Figure 4 Diagnostic algorithm for primary eosinophilia ($\geq 1.5 \times 10^9 l^{-1}$ blood eosinophil count). Key: CEL, chronic eosinophilic leukemia; HES, hypereosinophilic syndrome; FISH, fluorescent *in situ* hybridization; BM, bone marrow; PB, peripheral blood; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor. *T-cell receptor gene rearrangement studies and immunophenotyping.

natural history of molecular marker-positive but otherwise latent disease becomes better defined.[111–114]

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Appendix 1b

Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment

Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the international working group for myelofibrosis research and treatment

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To exploit the diagnostic usefulness of the recently discovered *JAK2* V617F mutation, as well as the characteristic bone marrow histopathological features reported in BCR-ABL-negative chronic myeloproliferative disorders, members of the International Working Group for Myelofibrosis Research and Treatment published revised diagnostic criteria for polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis.[1] The document was endorsed by the Clinical Advisory Committee for the revision of the WHO Classification of Myeloid Neoplasms and its adoption was recommended by the WHO.

Myelofibrotic transformation is a recognized complication of PV and ET, resulting in disorders now termed as post-PV myelofibrosis and post-ET myelofibrosis according to the revised nomenclature from International Working Group for Myelofibrosis Research and Treatment group.[2] However, specific diagnostic criteria for both post-PV and post-ET myelofibrosis, have yet to be defined. During the third international meeting of the International Working Group for Myelofibrosis Research and Treatment held in Houston, TX, on 25 May 2007, a panel of expert hematologists and hematopathologists addressed these issues for both clinical entities.

From a list of candidate criteria and by group consensus, the panel selected two required criteria for the diagnoses of post-PV myelofibrosis and post-ET myelofibrosis (Table 1). First, a verified diagnosis of pre-existing PV or ET was recommended as crucial for the diagnosis of MF transformation. Due to the

Table 1 IWG-MRT recommended criteria for post-PV MF and post-ET MF

Criteria for post-polycythemia vera myelofibrosis
Required criteria:
1 Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria[1]
2 Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,a]

Additional criteria (two are required):
1 Anemia[b] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
2 A leukoerythroblastic peripheral blood picture
3 Increasing splenomegaly defined as either an increase in palpable splenomegaly of ⩾5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4 Development of ⩾1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Table 1 (Continued)

Criteria for post-essential thrombocythemia myelofibrosis
Required criteria:
1 Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria[1]
2 Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,a]

Additional criteria (two are required):
1 Anemia[b] and a ⩾2 mg ml^{-1} decrease from baseline hemoglobin level
2 A leukoerythroblastic peripheral blood picture
3 Increasing splenomegaly defined as either an increase in palpable splenomegaly of ⩾5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
4 Increased LDH (above reference level)
5 Development of ⩾1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Abbreviations: IWG-MRT, International Working Group for Myelofibrosis Research and Treatment; LDH, lactate dehydrogenase; post-ET MF, post-essential thrombocythemia myelofibrosis; post-PV MF, post-polycythemia vera myelofibrosis.
[a]Grade 2–3 according to the European classification:[3] diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification:[4] diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.
[b]Below the reference range for appropriate age, sex, gender and altitude considerations.

insufficient discriminatory power of previous polycythemia vera study group (PVSG) diagnostic criteria,[1] and in particular, due to similarities of ET with prefibrotic primary myelofibrosis, the panel recommended that the previous diagnosis of PV or ET should fulfill the WHO criteria.[1] Second, careful bone marrow morphological examination is crucial in the diagnostic workup, since appearance of bone marrow fibrosis was recommended as a necessary criterion. Grade 2 or greater bone marrow fibrosis, according to the new European classification[3] or grade 3 or greater according to the standard classification,[4] was a prerequisite for the diagnosis. No other bone marrow morphological appearances were considered useful for the diagnosis of PV or ET evolving into MF. In addition to the above-mentioned two required criteria, the International Working Group for Myelofibrosis Research and Treatment recommends the presence of two additional criteria, as outlined in Table 1, for post-PV myelofibrosis and post-ET myelofibrosis.[5] We recommend that these criteria be incorporated in the revised WHO document and be utilized in both routine clinical practice and future clinical investigations.

G Barosi[1], RA Mesa[2], J Thiele[3], F Cervantes[4], PJ Campbell[5], S Verstovsek[6], B Dupriez[7], RL Levine[8], F Passamonti[9], J Gotlib[10], JT Reilly[11], AM Vannucchi[12], CA Hanson[2], LA Solberg[13], A Orazi[14] and A Tefferi[2], On behalf of the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT)

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2 Mesa RA, Verstovsek S, Cervantes F, Barosi G, Reilly JT, Dupriez B *et al.* Primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (post-PV MF), post essential thrombocythemia myelofibrosis (post-ET MF), blast phase PMF (PMF-BP): consensus on terminology by the international working group for myelofibrosis research and treatment (IWG-MRT). *Leuk Res* 2007; **31**: 737–740.
3 Thiele J, Kvasnicka HM, Facchetti F, Franco V, van der Walt J, Orazi A. European consensus on grading bone marrow fibrosis and assessment of cellularity. *Haematologica* 2005; **90**: 1128–1132.
4 Manoharan A, Horsley R, Pitney WR. The reticulin content of bone marrow in acute leukaemia in adults. *Br J Haematol* 1979; **43**: 185–190.
5 Cervantes F, Alvarez-Larrán A, Talarn C, Gómez M, Montserrat E. Myelofibrosis with myeloid metaplasia following essential thrombocythemia: actuarial probability, presenting characteristics and evolution in a series of 195 patients. *Br J Haematol* 2002; **118**: 786–790.

[redacted]

Appendix 3

Information regarding effectiveness of contraceptive methods

Females of childbearing potential will be requested to use the combination of two highly effective contraception methods.

For female patients participating in the study:

Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception throughout the study duration inclusive of 30 day safety follow up. Highly effective contraception methods include:

* Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

* Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

* Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.

* Combination of any two of the following (a+b or a+c, or b+c):

a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

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

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks 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.

Appendix 4

Drugs that interfere with coagulation or inhibit PLT function.

Antiplatelet Agents	Anticoagulant Agents	Procoagulant Agents	Synthetic inhibitors of factor Xa	Thrombolytic Agents	Direct thrombin inhibitors	NSAIDs and Acetaminophen	Food supplements
Aspirin (more than 125 mg/day)	Heparin	Aminocaproic Acid	Fondaparinux	Urokinase	Argatroban	Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Flurbiprofen, Oxaprozin, Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone, Piroxicam, Meloxicam, Tenoxicam, Droxicam, Lornoxicam, Isoxicam, Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid	Nattokinase (extracted and from a Japanese food called natto)
Ticlopidine	Warfarin	Desmopressin	Idraparinux	Streptokinase	Lepirudin		
Clopidogrel	Dicumarol			Anistreplase	Bivalirudin		Lumbrokinase (present in the earthworm *Lumbricus bimastus*)
Prasugrel	Phenprocoumon			Tissue plasminogen activators (t-Pa): Alteplase Reteplase Tenecteplase	Dabigatran		
Cilostazol	Acenocoumarol						
Abciximab	Anisindione						
Eptifibatide	Dalteparin						
Tirofiban	Danaparoid						
Dipyridamole	Enoxaparin						
Epoprostenol	Tinzaparin						
	Phenindione						

Appendix 5

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)

(Ferenci et al 2002)

Appendix 6

MDRD-eGFR Formula

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

Appendix 7

CYP3A4 inhibitors and inducers

Medications that can induce CYP3A4

Strong inducers	Moderate inducers	Weak inducers	Unclassified inducers
avasimibe	bosentan	amprenavir	topiramate
carbamazepine	efavirenz	aprepitant	
phenobarital	etravirine	armodafinil (R-modafinil)	
phenytoin	modafinil	dexamethasone	
rifabutin	nafcillin	echinacea	
rifampin	ritonavir	garlic	
St. John's wort	talviraline	gingko	
	tipranavir	glycyrrhizin	
		methylprednisolone	
		nevirapine	
		oxcarbazepine	
		pioglitazone	
		prednisone	
		pleconaril	
		rufinamide	
		troglitazone	

Note:

Inducer classification:

- Strong inducers may result in a substrate AUC decreased by ≥ 80%.
- Moderate inducers may result in a substrate AUC decreased by 50-80%.
- Weak inducers may result in a substrate AUC decreased by 20-50%.

This list is compiled based on the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 30 August 2010) for update or more details.

Medications that can inhibit CYP3A4

Strong inhibitors	Moderate inhibitors	Weak inhibitors
clarithromycin	amprenavir	alprazolam
conivaptan	aprepitant	AMD070
indinavir	atazanavir	amlodipine
itraconazole	cimetidine	azithromycin
ketoconazole	ciprofloxacin	bicalutamide
lopinavir	darunavir	cranberry juice
mibefradil	diltiazem	chlorzoxazone
nefazodone	elvitegravir	cilostazol
nelfinavir	erythromycin	cyclosporine
posaconazole	fluconazole	fluvoxamine
ritonavir	grapefruit juice	ginkgo
saquinavir	imatinib	goldenseal
telithromycin	schisandra sphenanthera	isoniazid
troleandomycin	tipranavir	lacidipine
voriconazole	tofisopam	M100240
	verapamil	nilotinib
		oral contraceptives *(e.g. drospirenone, norgestimate, and ethinyl estradiol)*
		peppermint oil
		propiverine
		ranitidine
		ranolazine
		roxithromycin
		Seville orange juice
		sitaxentan
		tabimorelin

Note:
Inhibitor classification:

- Strong inhibitors may result in a substrate AUC > 5-fold increase.
- Moderate inhibitors may result in a substrate AUC ≥ 2-fold increase and < 5-fold increase.
- Weak inhibitors may result in a substrate AUC ≥ 1.25-fold increase and < 2-fold increase.

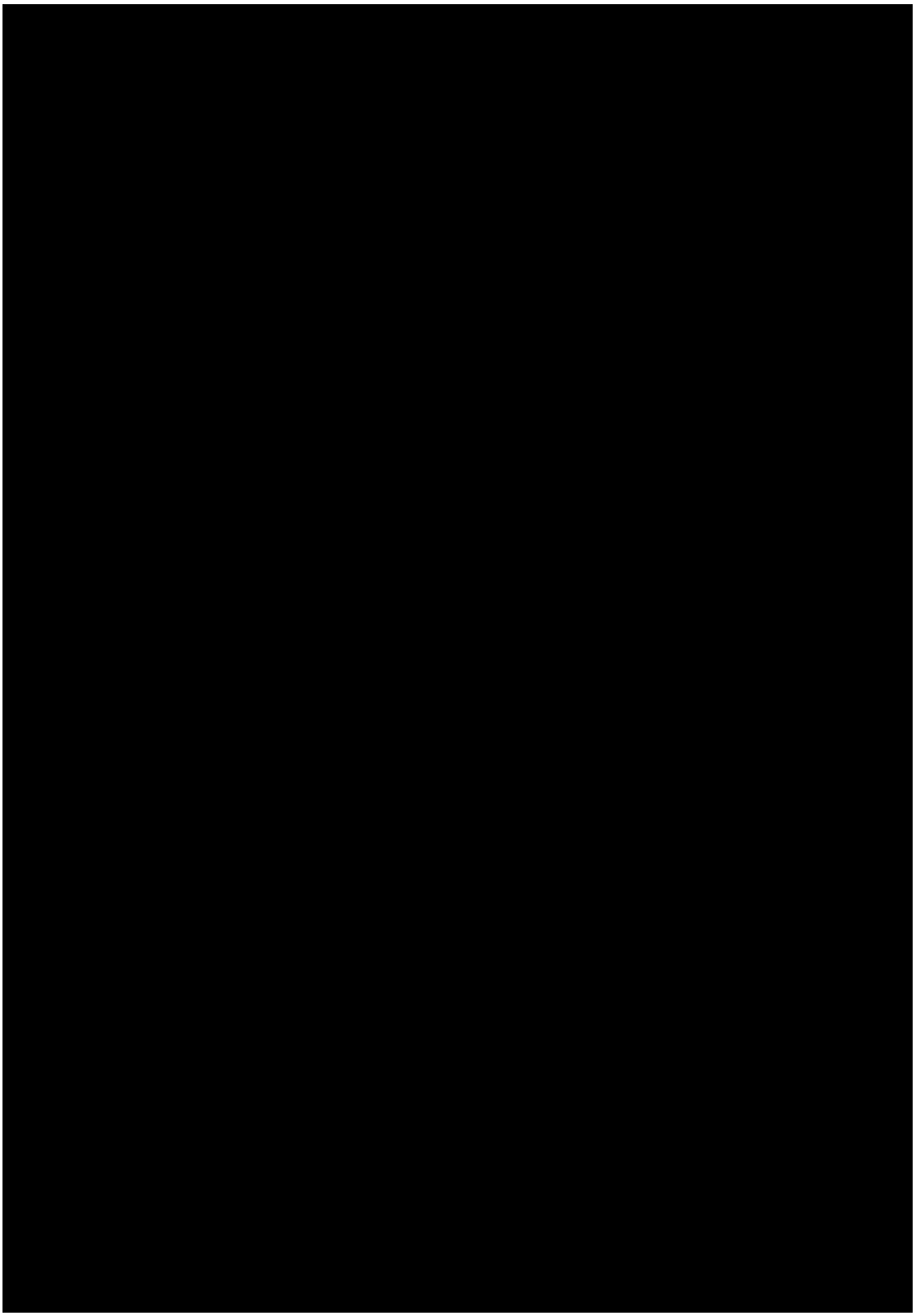
This list is compiled based on the FDA's "Guidance for Industry, Drug Interaction Studies", the Indiana University School of Medicine's Drug Interactions Database, and the University of Washington's Drug Interaction Database. This list may not be comprehensive and may be updated periodically. Refer to Novartis Oncology Clinical Pharmacology Internal Memorandum, Drug-drug interactions (DDI) Database (last updated 30 August 2010) for update or more details.

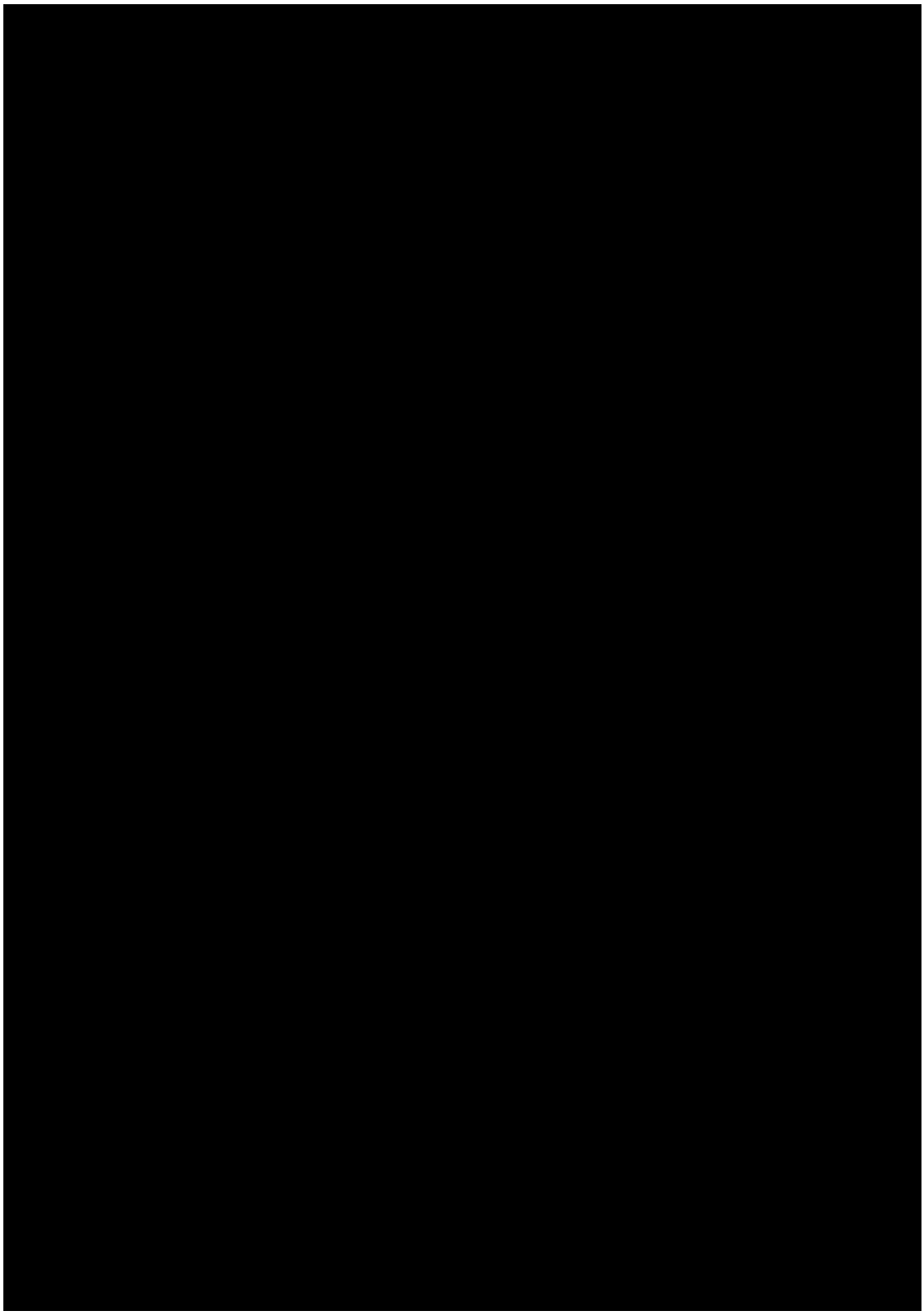
Appendix 8

New York Heart Association (NYHA) Functional Classification

NYHA Class	Symptoms
I	No symptoms and no limitation in ordinary physical activity. E.g., shortness of breath when walking, stair climbing, etc.
II	Mild symptoms (mild shortness of breath and/or angina pain) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (e.g. walking short distances, ~ >20 - 100m). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest, mostly bed bound patients

[redacted]





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Appendix 11

Eastern Cooperative Oncology Group (ECOG) 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 al1982)

Appendix 12

Clinical Laboratory Tests

Serum Chemistry	Hematology	Coagulation
ALT	Complete Blood Count (CBC)	INR
AST		
Alkaline phosphatase	Differential including reporting of % blasts	PTT
Total bilirubin		D-dimer or FDP
Direct bilirubin		
Albumin	Platelets	Fibrinogen
Lactate dehydrogenase		
Creatinine		
BUN		
Sodium		
Potassium		
Glucose		
Calcium		
Uric acid		
Other		
Pregnancy Test: Female patients of childbearing potential only; serum test at Screening and Follow-up. Urine test at subsequent visits per the Description of Study Visits (Section 6)		

Appendix 13

Prior calibration, hypothetical dose escalation scenarios, and operating characteristics of the Bayesian logistic regression model

Statistical models and dose recommendation

An adaptive Bayesian logistic regression model (BLRM) guided by the escalation with overdose control (EWOC) principle will guide the dose-escalation to determine the maximal safe starting dose (MSSD) of INC424. The model will use accumulated data on observed DLTs at each dose level and stratum. Bayesian inference will be used to assess the risks of overdose at each dose level. The use of Bayesian response adaptive models for Phase I studies has been advocated by the European Medicines Agency (EMA) guideline on small populations (2006) and by (Rogatko et al 2007) and is one of the key elements of the Food and Drug Administration's (FDA) Critical Path Initiative. For this trial a 3-parameter Bayesian logistic regression model will be used in order to establish the safety of oral INC424 treatment in patients with myelofibrosis and platelet counts between 50 $x10^9$/L and 100 $x10^9$/L.

INC424 is currently being evaluated in two randomized, pivotal studies, [INCB18424-351] and [INCB18424-352], in patients with myelofibrosis and baseline platelet counts > 100 $x10^9$/L. In these trials, the starting dose of INC424 is platelet dependent: patients with platelet counts between 100 $x10^9$/L and 200 $x10^9$/L begin at 15 mg b.i.d., and patients with platelet counts > 200 $x10^9$/L begin at 20 mg b.i.d.

The doses used in the above mentioned pivotal studies were determined based on data collected in a Phase I/II, dose-finding study, [INCB18424-251]. In [INCB18424-251], a total of 154 patients at a total of 8 different starting doses were explored, both in b.i.d. and q.d. schedules. Table A provides a summary of the number of patients treated at each of the 4 starting b.i.d. dose levels (n = 117), and Table B provides the patient-level data used to derive this summary. In addition, the total number of patients with a "DLT" (as defined in this current protocol [CINC424A2201]) was retrospectively determined. It is this retrospectively applied DLT definition that is summarized in Table A and Table B.

Table A Incidence of DLTs by starting dose level in the Phase I/II study [INCB18424-251] for patients who started on a b.i.d. regimen, where DLT is defined as in the current protocol

Dose schedule	Total daily dose (mg)	No of patients	No (%) of patients with DLTs
b.i.d.	20 mg	30	4 / 30 (13.3)
	30 mg	35	4 / 35 (11.4)
	50 mg	47	17 / 47 (36.2)
	100 mg	5	1 / 5 (20.0)

Table B DLT data from all patients starting at a b.i.d. dose schedule in Study [INCB18424-251]. Data provided are baseline platelet count (x10^9/L) and an indicator variable for observation of a DLT per the current study criteria (1 = yes, 0 = no)

Total daily dose 20 mg	Total daily dose 30 mg	Total daily dose 50 mg	Total daily dose 100 mg
476,0	226,0	998,1	319,0
174,0	318,1	647,0	611,0
372,0	667,0	360,0	151,0
268,0	283,1	298,0	102,1
113,0	639,0	454,0	394,0
125,1	245,0	170,1	
761,0	605,0	214,1	
231,0	208,0	426,0	
115,0	468,0	163,0	
574,0	240,0	285,0	
162,0	593,0	116,1	
483,0	478,0	277,0	
119,0	637,0	805,1	
130,0	624,0	871,0	
156,1	211,0	810,0	
117,0	285,0	832,0	
103,0	425,0	170,1	
424,0	622,0	210,1	
208,0	288,0	148,0	
596,0	209,0	118,0	
444,1	454,0	286,0	
336,0	237,0	138,0	
425,0	317,0	1195,1	
218,0	304,0	193,0	
133,0	231,0	223,0	
223,0	602,0	483,0	
123,0	544,0	214,0	
153,0	247,0	184,0	
195,0	449,0	147,1	
147,1	683,0	118,1	
	379,0	245,1	
	468,1	415,1	
	316,0	138,0	
	351,0	315,1	
	220,1	372,0	
		372,0	
		202,0	
		168,0	

Total daily dose 20 mg	Total daily dose 30 mg	Total daily dose 50 mg	Total daily dose 100 mg
		380,1	
		131,0	
		215,0	
		338,1	
		263,0	
		202,1	
		324,0	
		250,0	
		343,1	

After the patients in each cohort have completed at least 28 days of treatment, the prior distribution will be updated with the accumulated DLT data. Posterior probabilities for the rate of DLT by stratum will be summarized from the model. Selection of the next dose will be based on these probabilities as well as on other safety and laboratory data.

See Section 9.4.2 of the protocol for BLRM and for an elaborate explanation of the derivation of the prior.

Hypothetical dose escalation scenarios

In order to show how the Bayesian model reacts, different hypothetical scenarios were investigated. The designs should make reasonable decisions during a study based on the observed toxicities particularly in early cohorts. Table C shows on-study decisions made for each of 4 different specified hypothetical DLT observations based on the BLRM. Note that per the protocol design, stratum 2 does not begin enrollment until dose level 3 (total daily dose = 20 mg) has been declared open in stratum 1.

Table C Hypothetical dose escalation scenario (S1 = Stratum 1, S2 = Stratum 2)

Scenario	Cohort	Total Daily Dose Received	Number of DLTs / Number of patients	Recommended Total Daily Dose (mg) for Next Cohort
1	1 (S1)	10 mg (S1)	0 / 3 (S1)	15 mg (S1)
	2 (S1)	15 mg (S1)	≤ 1 / 3 (S1)	20 mg (S1), 10 mg (S2)
	3 (S1), 1 (S2)	20 mg (S1), 10 mg (S2)	≤ 1 / 3 (S1), 0 / 3 (S2)	25 mg (S1), 15 mg (S2)
2 (all S1)	1	10 mg	1 / 3	10 mg
	2	10 mg	1 / 3	10 mg
	3	10 mg	≥ 1 / 3	STOP
3 (all S1)	1	10 mg	≥ 2 / 3	STOP
4 (all S1)	1	10 mg	0 / 3	15 mg
	2	15 mg	2 / 3	10 mg
	3	10 mg	0 / 3	15 mg
	4	15 mg	1 / 3	15 mg

Simulated operating characteristics

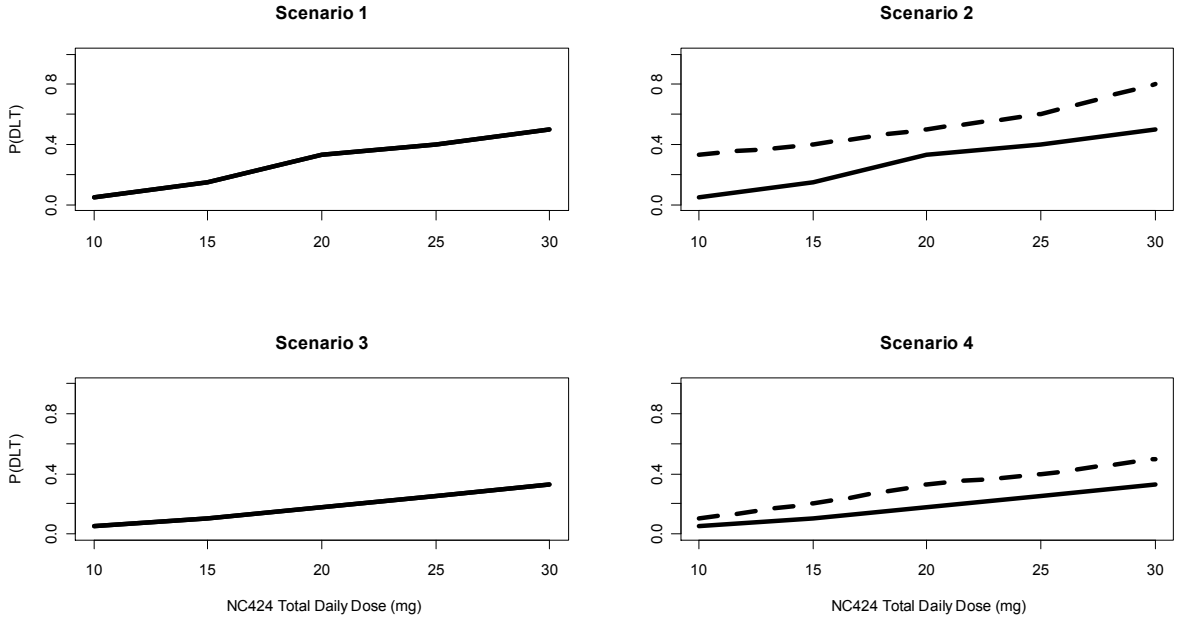
In the previous Section, some individual hypothetical scenarios were investigated to understand how the BLRM reacts within a clinical trial. In this Section, the performance of the BLRM over many trials is investigated via simulation. This approach allows for an understanding of how the BLRM behaves on average based on an assumed "truth", i.e., assuming the true underlying relationship between dose and probability of DLT were known.

Hypothetical true relationships between dose and probability of DLT

A total of 4 different true relationships between dose and probability of DLT [P(DLT)] were assumed. For each scenario, the relationship between dose and P(DLT) is specified for each stratum.

Figure A displays the assumed P(DLT) for INC424 doses for the four scenarios. For scenarios 1 and 3, no stratum effect is assumed.

Figure A Dose-DLT relationship of the different scenarios (solid line = stratum 1, dashed line = stratum 2)



Simulation parameters

A total of 1000 trial simulations were used for each scenario and the total minimum number of DLTs to control the declaration of MSSD was fixed to one. No more than 1 dose level was allowed to be increased in single step.

The number of patients to enroll in each cohort and stopping rules used to declare MSSD were defined as:

- Cohort size: 3
- Approximate number of patients enrolled: 31

- Minimum number of patients treated at the recommended MSSD: 9

Metrics

Operating characteristics were reviewed for the simulations to compare the relative performance under each true scenario. The metrics reviewed were:

- Probability of recommending a target dose as the MSSD (correct final decision) (I)
- Probability of recommending a dose with true P(DLT) ≥ 33.3% as the MSSD (patient risk) (II)
- Probability of recommending a dose with true P(DLT) < 16% as the MSSD (III)
- MSSD < smallest positive dose (i.e. 10mg) (IV)
- Average proportion of patients receiving a target dose on study (V)
- Average proportion of patients receiving a dose with true P(DLT) ≥ 33.3% on study (VI)
- Average proportion of patients receiving a dose with true P(DLT) < 16% on study (VII)
- Average number of patients per study (VIII)

Results

The simulated operating characteristics presented below show that the model performs well under the wide range of hypothetical scenarios investigated.

Table D and Table E summarize the results from the simulations performed for both strata.

Table D Summary metrics of simulations for Stratum 1

Scenario	I	II	III	IV	V	VI	VII	VIII
1	.537	.306	.146	.011	.327	.308	.365	21
2	.362	.074	.418	.146	.309	.146	.545	18
3	.961	0	.012	.027	.723	0	.276	21
4	.963	0	.018	.019	.711	0	.289	21

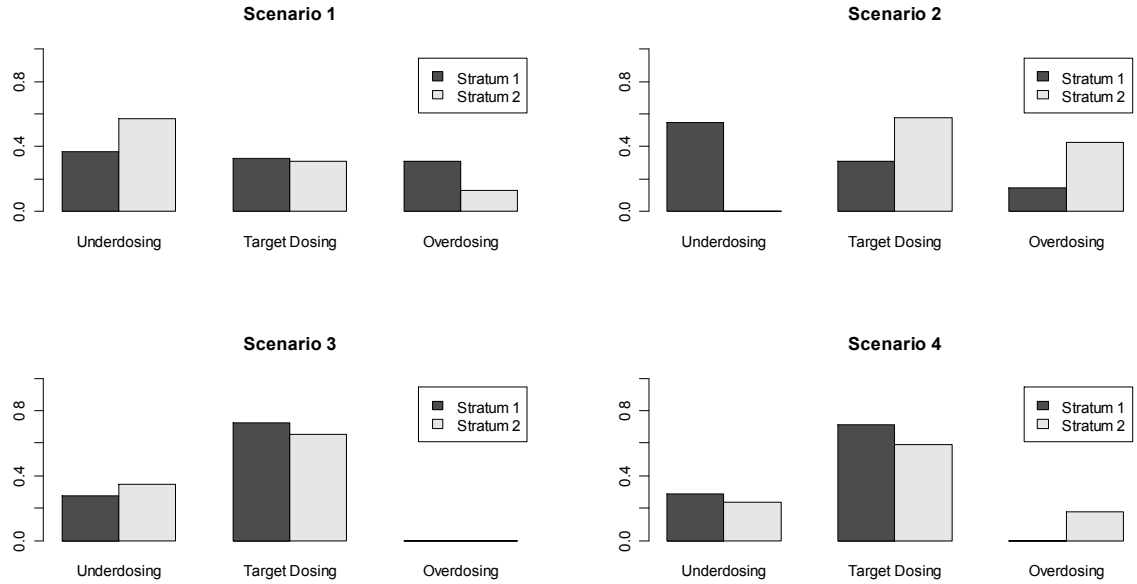
Table E Summary metrics of simulations for Stratum 2

Scenario	I	II	III	IV	V	VI	VII	VIII
1	.358	.064	.475	.103	.306	.126	.568	18
2	.143	.125	0	.732	.575	.426	0	9
3	.841	0	.073	.086	.655	0	.345	20
4	.674	.136	.047	.143	.589	.176	.235	18

Figure B shows the proportions of patients receiving INC424 falling into the different toxicity intervals for the four hypothetical scenarios. In this figure, the proportion of patients treated in the targeted toxicity interval is 33%, 31%, 72% and 71% for scenarios 1, 2, 3 and 4, respectively, in stratum 1, and 31%, 58%, 66%, and 59%, respectively, in stratum 2. The proportion of patients treated in the over-dosing interval is higher than 25% in 2 situations. In Scenario 1, stratum 1, 31% of patients are treated in the over-dosing interval. This is due to the relatively low P(DLT) that is possible in this interval (40%). In Scenario 2, stratum 2, 43% of patients are treated in the over-dosing interval. However, this is due to the simulation

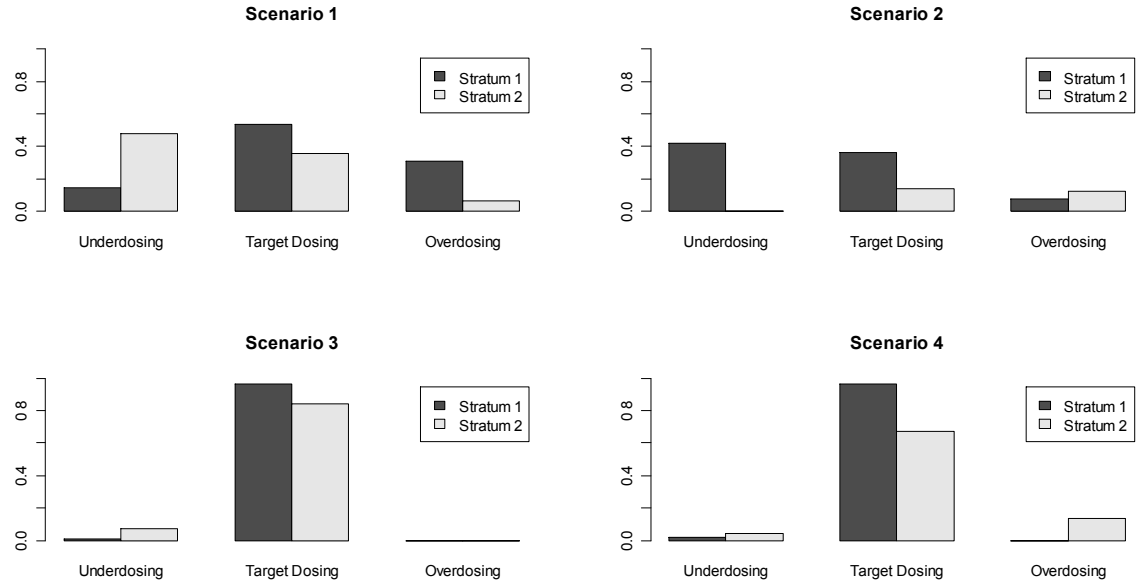
assumption that all doses in the study are in the overdosing interval. This assumption is extreme since it assumes a greater than 9 times odds of DLT at the first dose level for patients in stratum 2 relative to stratum 1. Most of the simulations (72%) for this scenario in this stratum resulted in [correctly] declaring an MSSD that was below the range under study.

Figure B Proportions of patients receiving targeted dose, who are under-dosed or who are over-dosed



The MSSD dose selections under the four hypothetical scenarios are presented in Figure C. The MSSD dose selection in the over-dosing interval occurs in less than 25% in all but 1 of the strata in one of the scenarios (Scenario 1, stratum 1), where it is 30.6%. This is due to the underlying DLT probability rate in the lowest dose in the over-dosing interval, where the P(DLT) is 40%.

Figure C MSSD dose selection under different dose-toxicity scenarios



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