NOVARTIS

Clinical Development

INC424 (ruxolitinib)

Protocol CINC424A2401 / NCT01493414

# An open-label, multicenter, expanded access study of INC424 for patients with primary myelofibrosis (PMF) or post polycythemia myelofibrosis (PPV MF) or post-essential thrombocythemia myelofibrosis (PET-MF)

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## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| βhCG | Beta human chorionic gonadotropin |
| alloHSCT | Allogeneic hematopoietic stem cell transplantation |
| ALT | Alanine aminotransferase/glutamic pyruvic transaminase/GPT |
| ANC | Absolute neutrophil count |
| AST | Aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT |
| AUC | Area under the concentration time curve |
| b.i.d./BID | *bis in diem*/two times per day |
| BAT | Best available therapy |
| BSC | Best supportive care |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CI | Clinical improvement |
| $C_{max}$ | Maximum concentration |
| CML | Chronic myeloid leukemia |
| COMFORT | COntrolled MyeloFibrosis Study With ORal JAK Inhibitor Treatment |
| CR | Complete response |
| 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 |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CYPs | Cytochrome P450 system of metabolizing enzymes, includes isoenzymes designated CYP3A4, CYP2C11, CYP2C13 |
| DAR | Dosage Administration Record |
| dL | Deciliter (100 mL) |
| DS&E | Drug safety and epidemiology |
| EAP | Expanded access protocol |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form; the term eCRF can be applied to either EDC or Paper |
| EDC | Electronic Data Capture |
| EOT | End of treatment |
| EPO | Erythropoietin |
| ESA | Erythropoietic stimulating agent |
| ET | Essential thrombocythemia |
| FACIT-Fatigue | Functional Assessment of Chronic Illness Therapy-Fatigue Scale |
| FACT-lym | Functional Assessment of Cancer Therapy for patients with Lymphoma |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| FLT3 | Fms-like tyrosine kinase 3 |
| FPFV | First patient first visit |
| FPLV | First patients last visit |

[redacted]

| | |
|---|---|
| FSH | Follicle stimulating hormone |
| GCP | Good clinical practice |
| G-CSF | Granulocyte colony-stimulating factor |
| GI | Gastrointestinal |
| HDAC | Histone deacetylase |
| HDL | High density lipoprotein |
| HEENT | Head, eyes, ears, nose, throat |
| Hgb | Hemoglobin |
| HIV | Human immunodeficiency virus |
| HRQOL | Health-related quality of life |
| HU | Hydroxyurea |
| i.v. | intravenous(ly) |
| IB | Investigator's brochure |
| IC | Inhibitory concentration |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IMS | Integrated Medical Safety |
| INR | International normalized ratio |
| IRB | Institutional Review Board |
| IRT | Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System |
| IUD | Intrauterine device |
| IUS | Intrauterine system |
| JAK | Janus kinase |
| JUMP | JAK Inhibitor ruxolitinib in myelofibrosis patients |
| L | Liter |
| LFS | Leukemia-free survival |
| LFTs | Liver function tests |
| LPFV | Last patient first visit |
| MAA | Marketing Authorization Application |
| MedDRA | Medical dictionary for regulatory activities |
| MF | Myelofibrosis |
| MFSAF | Modified Myelofibrosis Symptom Assessment Form |
| Mg | Milligram(s) |
| MID | Minimally important difference |
| mL | Mililiter(s) |
| MPD | Myeloproliferative disorder |
| MPN | Myeloproliferative neoplasms |
| MRI | Magnetic resonance imaging |
| MRU | Medical resource utilization |
| MSDS | Material Safety Data Sheet |
| NDA | New Drug Application |
| NOAEL | No-observed-adverse-effect level |
| o.d. | *omnia die*/once a day |
| ORR | Overall response rate |
| p.o. | *per os*/by mouth/orally |

[redacted]

| | |
|---|---|
| p.o. | *per os*/by mouth/orally |
| PD | Progressive disease |
| PE | Physical examination |
| PET-MF | Post essential thrombocythemia-myelofibrosis |
| PFS | Progression free survival |
| PHI | Protected health information |
| PMF | Primary myelofibrosis |
| PPV-MF | Post polycythemia vera-myelofibrosis |
| PS | Performance status |
| pSTAT3 | Phosphorylated signal-transducer and activator of transcription 3 |
| PT | Prothrombin time |
| PTT | Partial thromboplastin time |
| PV | Polycythemia vera |
| QAM | Once in the morning |
| QoL | Quality of life |
| QPM | Once in the evening |
| RAP | The Report and Analysis Plan (RAP) is a regulatory document which provides evidence of preplanned analyses |
| RDC | Remote data capture |
| REB | Research Ethics Board |
| SAE | Serious Adverse Event |
| SD | Stable disease |
| SOP | Standard Operating Procedure |
| SPA | Special Protocol Assessment |
| STAT | Signal transducers and activators of transcription |
| $T_{1/2}$ | Half life |
| $T_{max}$ | Time to maximum concentration |
| TOI | Trial outcome index |
| ULN | Upper limit of normal |
| USA | United States of America |
| VS | Vital signs |
| WBC | White blood cell count |

[redacted]

## Glossary of terms

| | |
|---|---|
| Assessment | A procedure used to generate data required by the study |
| 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 | Drug 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 in within approved indication/dosage |
| 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 center number, a unique identifier is created for each patient in the study and will be on the study drug dispensing label |
| Period | A subdivision of the study timeline; divides stages into smaller functional segments such as screening, baseline, titration, washout, etc. |
| Premature patient withdrawal | Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; 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 |
| Stage related to study timeline | A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc. |
| Stop study participation(End of treatment) | Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later |
| Study treatment | Includes any drug or combination of drugs in any study arm administered to the patient (subject) as part of the required study procedures, including placebo and active drug run-ins.<br>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 premature patient withdrawal |
| Variable | Identifier used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points |

[redacted]

# Amendment 5

## Amendment Rationale

The primary purpose of the amendment is to align this protocol with the latest modified Novartis standard language for clinical study protocols:

- Updated highly effective contraception method

  The "contraception use" wording has been updated to provide clarification and implement latest available guidelines as to highly effective contraception. Since all patients are enrolled, the clarification does not apply per se to exclusion criteria but may be used as needed for female of childbearing potential currently enrolled in the trial.
- Updates to concomitant therapy and prohibited concomitant therapy

  Clarifications to concomitant therapy and prohibited concomitant therapy is also updated in appendix.
- Additional changes:

  Reticulocytes count and coagulation parameters determination may or may not be part of the standard evaluation performed in clinical practice at different health care centers. As this study aims to resemble the use of ruxolitinib in patients with myelofibrosis in the clinical practice setting, we will allow optional collection and results reporting in the CRF when collected and deemed clinically relevant on a patient basis.

**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 and bold for insertions.

1. Updated author list of protocol [redacted] to reflect the team currently working on/managing the protocol.
2. Study synopsis:
   a. Background

      Newer wording and included the EMA approval date.
   b. Study design

      Updated end recruitment as 31-Dec-2014
   c. Inclusion/ Exclusion - exclusion criteria

      Exclusion criteria #15 as to Childbearing potential updated to reflect latest international guidance related to highly effective contraception
   d. Dose, Regimen, Treatment

      Clerical update: added Table 6-2 reference as in the protocol
3. Section 1 Background

   Updated wording: approved by the EMA on 31-Aug-2012
4. Section 1.1 Overview of myelofibrosis and myeloproliferative neoplasms and current treatment options

   Updated newest information and Figure 1-1
5. Section 1.3 Overview of INC 424

[redacted]

Updated wording to reflect latest information on JAK pathway and approval of Jakavi in 90 counties.

6. Section 1.3.1 INC 424 Pharmacokinetics
   Updated section with recent information as to current study results.
7. Section 1.3.3 INC 424 clinical safety in healthy volunteers
   Included recently updated study information.
8. Section 1.3.4.1 Phase I/II study of INC 424 in patients with primary, post-PV, or post ET MF
   Figure renumbered to Figure 1-2a and Figure 1-2b.
9. Section 1.3.5 Phase III INC424 clinical trials (controlled MF study with oral JAK inhibitor treatment [COMFORT; (INCB 18424-351 and CINC424A2352)])
   Clinical update information with COMFORT I and II
10. Section 4.1 Descrition of Study Design
    Updated to current study status 2238 patients enrolled and enrollment ended 31 Dec 2014.
11. Section 5.1 Patient population
    Updated wording to clarify the understanding of the pharmacokinetics and interactions that physicians should be aware that CYP3A4 is an isoenzyme that can catalyze a biotransformation of INC424.
12. Section 5.3 exclusion criteria 15.
    Updated wording to new standard Childbearing potential wording.
13. Section 6.2.2.3 Dose modification for Renal Impairment
    Clarified wording that no specific dose adjustment is needed in patients with mild or moderate renal impairment.
14. Section 6.2.2.4 Dose modification for hepatic impairment
    Update wording to monitor and reduce dose to avoid adverse drug reactions
15. Section 6.2.4 Dose Reduction for concomitant CYP Inhibitor Usage
    Update wording to clarify more frequent monitoring to prevent events with strong potent CYP3A4 inhibitors.
16. Section 6.2.5 Optional dose tapering strategy in the event of study drug discontinuation
    Wording to clarify possible events symptoms due to abruptly stopping ruxolitnib.
    Wording explaining concomitant use of corticosteroids prior to or during the dose tapering.
17. Section 6.2.6.1 Dose reduction for non-hematological safety
    New section created as to non hematological safety recommendation and dosing recommendation for these events.
18. Section 6.3 Concomitant Medication
    Addition of a general sentence as to timeframe for collection in EDC of concomitant medication and general warning about use of concomitant medication during trial.
19. Section 6.3.1 Permitted Concomitant Therapy
    New standard language added natural and herbal treatments allowed.
20. Section 6.3.2 Permitted Concomitant therapy requiring caution and or action

[redacted]

Updated wording to explain guidance in the referenced appendix and precision added as to use of topical ketoconazole not requiring ruxolitinib dose adjustement.

21. Section 6.3.3 Prohibited Concomitant Therapy

    Update wording in the guidance of the referenced appendix

22. Table 7-2 Laboratory assessment

    As not being standard tests performed in clinical setting for patients's follow up, reticulocytes assessment will be optional. Coagulation laboratory assessments are also optional after enrollment. The investigator may continue to draw labs if considered clinically significant to maintain safety evaluation on patients.

23. Section 7.3 Screening

    INR added to the Coagulation to be consistant with the table 7.2

24. Section 7.5.1.3, Section 7.5.1.5, Section 7.5.1.7, Section 7.5.1.9, Section 7.5.1.11, Section 7.5.1.13, Section 7.5.1.15, Section 7.6.3.1

    Coagulation parameters are optional for these follow up visits.

25. Section 8.2.9 Clinical Safety laboratory assessments

    Wording made consistent hematology reticulocytes are optional and coagulation laboratory assessments are optional after enrollment.

26. Section 9.1.1 Safety Definitions and reporting disease progression

    Wording clarified as to reportable and exempted events related to disease progression. All events not related to disease progression should be reportedevents.

27. Section 9.1.1.2 Events related to the disease

    Updated wording to clarify to the investigator when reporting worsening of symptoms (AE), the causality of an AE may be related to the study drug or related to the disease

28. Section 9.1.1.2 Surgical procedure

    Wording updated to clarify that planned surgical procedures do not have to reported as an AE

29. Section 9.1.2 Definitions

    Confusing wording was updated to clarify protocol exempted SAE.

30. Section 11.6.1.1 Full Analysis set will be used for all efficacy analysis

    Clarified wording as no cycle of therapy are being done with ruxolitinib.

    Progression free survival, Leukemia free survival and Overall survival are clarified as to period of time until which data will be taken into account. Protocol mandating a 28 to 37 days follow up, data will not be considered if collected and reported after this timeframe.

31. Section 13 References

    Updated references related to the updated sections referenced.

32. Appendix II

    Updated with new standard language for highly effective contraception.

33. AppendixIII

    Updated: Hematology reticulocytes absolute and % are optional and

    Coagulation parameters are optional after enrollment.

34. Appendix VI

[redacted]

Updated to the most recent Novartis guidance.

Steroids are allowed for use during trial as described in protocol. Steroids are deleted from list of prohibited medication to align with protocol requirements.

35. Appendix X

    Enrollment being closed from end 2014, eligibility checklist is no longer used and not kept to avoid confusion with updated highly effective contracetion measures update that will be implemented from Amendment 05 approval.

## IRB/IEC 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.

[redacted]

## Amendment 4

### Amendment rationale

Sanofi announced on November 18th 2013 the decision to halt all clinical trials and cancel plans for regulatory filings with its investigational JAK2 inhibitor, fedratinib (SAR302503). Fedratinib is a novel, investigational JAK2 inhibitor that was under development for the treatment of myelofibrosis, including those previously treated with ruxolitinib.

The decision follows reports of cases consistent with Wernicke's encephalopathy in patients participating in fedratinib clinical trials. Sanofi requested that study investigators discontinue fedratinib treatment for patients in all trials and notified health authorities worldwide.

To date, more than 16,000 patients have been treated with ruxolitinib worldwide as part of the clinical trial program and commercial usage. Novartis has conducted a search of the ruxolitinib worldwide safety database and have found no reported cases of Wernicke's encephalopathy in patients treated with ruxolitinib. Additionally, based on a search of scientific information currently available in the public domain, Novartis considers there is no evidence suggesting a relationship between the JAK/STAT pathway and Wernicke's encephalopathy.

Physicians having patients under treatment with fedratininb should determine with them the best alternative course of therapy for their myelofibrosis and if deemed appropriate consider a switch to ruxolitinib.

Acknowledging the urgent medical need for an active therapy that these patients have after discontinuing therapy with fedratinib and for countries where ruxolitinib is not commercially available, this amendment is deemed necessary to allow patients discontinued from fedratinib to have the opportunity to be treated with ruxolitinib if they wish so and if recommended by the treating physician and if inclusion/exclusion criteria are dully fulfilled.

The major changes to the protocol include:

1.0 Addition of inclusion criteria to allow fedratinib pretreated patients to be included in the trial as long as clinical, laboratory and image assessments are properly documented.

2.0 Update of visit schedule and assessments.

### Study Status

The trial is currently enrolling. As of December 2nd 2013, there are 1784 patients enrolled in the study.

### Changes to the protocol

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

1. Updated author list of protocol [redacted] to reflect the team currently working on/managing the protocol.
2. Study Synopsis

[redacted]

a. Study objective:
   - Primary objective: clarification that patients being previously treated by investigational drug may be part of the study population as described per initial and current inclusion/exclusion criteria.
   - Secondary objective: correction of typo, secondary objectives is to assess best overall response rate of INC424 in patients with PMF, PPV MF, or PET-MF as evaluated by investigator.

b. Study design.
   - Insertion of transplant as a reason for end of treatment.
   - Clarification that as based on country assessments and not computed, the maximum number of patients expected to be included in the trial is not 2484 but 2500.

c. Population.
   - Clarification that patients being previously treated by investigational drug may be enrolled as per original and current inclusion/exclusion criteria.

d. Sample size.
   - Clarification that as based on country assessments and not computed, the maximum number of patients expected to be included in the trial is 2500.

e. Inclusion/exclusion criteria
   - Addition of Inclusion criteria13 describing assessments and documentation for fedratinib pre-treated patients:
   - "Fedratinib pretreated patients with documented complete physical examination including full neurologic examination and cardiology assessment, thiamine level testing, and MRI of the brain if indicated based on signs or symptoms. Patients pretreated with fedratinib should have completed or be receiving thiamine supplementation according to the investigator's instructions."
   - Addition of Eclusion criteria describing assessments and documentation for fedratinib pre-treated patients:
   - Addition of information to Exclusion criteria 13: insertion of statement that patients previously treated by fedratinib within 14 days of screening are not eligible for the trial.
   - Addition of Exclusion criteria 19 defining exclusion criteria for ruxolitinib pre-treated patients if primary resistant to ruxolitinib, primary resistance being defined as:
   - No spleen reduction within the first 12 weeks after front line therapy with ruxolitinib. AND
   - No reduction in symptoms within the first 12 weeks after first-line treatment with ruxolitinib.
   - Addition of Exclusion criteria 20: in the case of ruxolitinib pretreated patients, patients discontinuing ruxolitinib due to a Grade 4 AE related or suspected to be related to ruxolitinib.

f. Patient numbering.

[redacted]

- Information about patient numbering for those patients who may have participate in CINC424A2401 before being under fedratinib: those patients will receive a new patient number as per usual process.

g. Dose, regimen, treatment.
   - As per previous protocol amendments, low platelet patient are defined as patients having from 50,000 to <100,000/µL platelet count. A correction is needed to update upper limit platelet count for patients starting with a 5mg BID regimen, platelet count for this starting dose is corrected from 99,000/µL to <100,000/µL.
   - Insertion of transplant as a reason for end of treatment.

h. Statistical methods and data analysis.
   - Addition of a Per Protocol set.
   - [redacted]

i. Interim analysis.
   - Upper limit platelet count for low platelet set have been updated from 99,000/µL to < 100,000/µL platelet count as defined for low platelet population.
   - Clarification that analysis may be performed if needed to fulfill regulatory obligation or to comply with post-approval commitments.

3. Section 2.1 Study rationale and purpose.
   - While regulatory approval is sought, there are no means available for patients with PMF, PPV MF, or PET-MF to receive INC424 outside of a clinical trial. Sentence "Patients who received prior treatment with commercially available agents or who have never received treatment do not have an access path to this new agent." is describing this same population and is deleted.
4. Section 2.2 Rationale and dose regimen selected.
   - Correction of low platelet term used for patient with 100,000 to 200,000 µL platelet count, based on additional information on efficacy and safety collected from original protocol and integrated in previous protocol amendments. Clarification that patients with platelet count from 50,000 to < 100,000µL are part of low platelet population and starting treatment at 5mg BID.
5. Section 3.1 Primary objective.
   - Clarification that patients being previously treated by investigational drug may be are part of the population as per original and current protocol design.
6. Section 4.1 Study design.
   - Insertion of transplant as a reason for end of treatment.
   - Clarification that recruitment will end once 2500 patients are enrolled or by 31Dec2014, whichever comes first.
7. Section 5.1 Patient population
   - Clarification that patients being previously treated by investigational drug may be enrolled as per original and current inclusion/exclusion criteria.
8. Section 5.2 Inclusion criteria

[redacted]

- Addition of Inclusion Criteria 13: fedratinib pretreated patients need to have a documented complete physical examination including full neurologic examination and cardiology assessment, thiamine level testing, and MRI of the brain if indicated based on signs or symptoms. Patients pretreated with fedratinib should have completed or be receiving thiamine supplementation according to the investigator's instructions.

9. Section 5.3 Exclusion criteria.
   - Addition of information as to fedratinib as previous investigational treatment in Exclusion criteria 13: insertion of statement that patients previously treated by fedratinib within 14 days of screening are not eligible for the trial.
   - Addition of Exclusion criteria 19, defining exclusion criteria for ruxolitinib pre-treated patients if primary resistant to ruxolitinib, primary resistance being defined as:
   - No spleen reduction within the first 12 weeks after front line therapy with ruxolitinib. AND
   - No reduction in symptoms within the first 12 weeks after first-line treatment with ruxolitinib.
   - Addition of Exclusion criteria 20: in the case of ruxolitinib pretreated patients, patients discontinuing ruxolitinib due to a Grade 4 AE related or suspected to be related to ruxolitinib.
10. Section 6.1.1 Study drug dosing
    - Insertion of transplant as a reason for end of treatment.
    - Clarification that patients with a Baseline platelet count from 50,000 to < 100,000/μL will begin dosing at 5 mg BID (one 5 mg tablet BID):
    - Deletion of "Patients with a Baseline platelet count of 50,000/ μL – 99,000/μL will begin dosing at 5 mg BID (one 5 mg tablet BID)" and insertion of sentence "Patients with a Baseline platelet count of 50,000/ μL to <100,000/μL will begin dosing at 5 mg BID (one 5 mg tablet BID)"
11. 6.2.2.1 Dose reduction for patients starting INC424 at doses 15-50 mg po BID.
    - Table 6.2: correction added to harmonize way platelet count are referred to in the table: 100 to <125,000/μL have been replaced by 100,000/μL to <125,000/μL. The correction have been done for all platelet counts displayed in the table.
12. 6.2.3.1 Restarting or reinstituting previous dose for patients who start INC424 15-20mg BID.
    - Table 6-4: correction added to harmonize way platelet count are referred to in the table: 100 to <125,000/μL have been replaced by 100,000/μL to <125,000/μL. The correction have been done for all platelet counts displayed in the table.
13. Section 6.4.1 Patient numbering.
    - Clarification on patient number assignment: no Interactive Response Technology system is used, patient number is attributed by site in sequential order and entered into RDC.

[redacted]

- Information regarding patient numbering for those patients who may have participated in CINC424A2401 before being under fedratinib: those patients will receive a new patient number as per usual process.

14. Section 6.5.2 Study drug packaging and labeling.
    - Clarification as regards to global or local supply of drug..
    - Insertion of transplant as a reason for end of treatment.
15. Section 7.1 Study flow and visit schedule.
    - Table 7.1: visit evaluation schedule:
    - Insertion of additional evaluations at screening:
    - insertion of full neurologic and cardiology assessments, to identify any signs or symptoms of thiamine deficiency or Wernicke's enchepalopathy.
    - insertion of MRI to be performed if clinically indicated (i.e. presence of clinical neurologic or psychiatric symptoms or physical examination findings or an history of established or suspected diagnosis of Wernicke's encephalopathy while under therapy with fedratinib.
    - Insertion of Eligibility checklist to be kept in source documentation

Table 7.2: Laboratory Assessment Schedule:

- Insertion of thiamin blood level assessment at screening.

16. Section 7.3 Screening.
    - Description of clinical patterns, blood evaluation and, if deemed appropriate based on clinical symptoms, MRI assessment for patients with a suspicion of Wernicke's Encephalopathy.
    - Addition of eligibility checklist to be completed and sent to Sponsor, approval is to be received back by Site before patient enrollment. This checklist is implemented as no IRT system is used.
17. Section 7.6.1 Criteria for premature withdrawal.
    - Clarification that patient with low platelet count are including patient with baseline platelet count from 50,000 to <100,000/µL : deletion of 50,000– 90,000/µL platelet count and update to 50,000 to <100,000/µL platelet count for sections related premature withdraw due to hematologic and non-hematologic toxicity.
18. Section 8.2.6 Full neurologic evaluation.
    - Incorporation of full neurologic examination and cardiology assessments to identify any signs and symptoms of thiamine deficiency or Wernicke's Encephalopathy for fedratinib pretreated patients:
    - For fedratinib pretreated patients there is a need to perform neurologic and cardiology examinations will be performed to identify any sign of thiamine deficiency or Wernicke's Encephalopathy which common symptoms or signs at disease presentation are: ocular abnormalities, mental status changes, and incoordination of gait and trunk ataxia. Uncommon symptoms or signs at presentation have to be also assessed: stupor, hypotension and tachycardia, hypothermia, bilateral visual disturbances and papilledema, epileptic seizures, hearing loss, hallucinations and behavioral disturbances.

[redacted]

19. Section 8.2.9 Clinical safety laboratory assessments.
    - Addition of thiamine blood level assessment as part of laboratory assessment for fedratinib pretreated patients.
20. Section 9.1.1 AE Definition and Reporting.
    - Clarification that monthly AE reporting to DSE will not be done and that reporting in place is corresponding to Good Vigilance Practice.
21. Section 10.3 Data collection.
    - Data collected will include information about previous fedratinib treatment as well as its end date when applicable. For pre-treated fedratinib patients, information regarding previous treatment by ruxolitinib will be collected, as well as if patient have been previously treated by ruxolitinib within CINC424A2401. If patient previously participated in CINC424A2401, his/her initial patient number will be collected.
22. Section 11.2 Populations for analysis.
    - Addition of a Per Protocol set.
23. Section 11.6.1.
    - Clarification that FAS will be used for all efficacy analysis.
24. Section 11.6.8.
    - [redacted]
25. Section 11.7 Interim analysis
    - Correction to include patients with platelet count from 50,000 to <100,000/µL in the population defined as low platelet patient: deletion of 99.000/µL and insertion of <100,000/µL as upper limit for platelet count for this population.
    - Clarification that analyses may be performed if needed to fulfill regulatory obligations, to comply with post-approval commitments or for publication purposes.
26. Section 11.8 Sample size calculation.
    - Clarification that as based on country assessments and not computed, the maximum number of patients expected to be included in the trial is 2500. Trial recruitment will end once 2500 patients included is reached or by 31 Dec 2014, whichever comes first.
27. Appendix III.
    - Addition of thiamine blood level assessment as part of laboratory assessment for fedratinib pretreated patients.
28. Appendix X.
    - Eligibility checklist.

[redacted]

## Amendment 3

## Amendment rationale

Since implementation of amendment version 02, dated 13Aug2012, updates from the EXPAND trial has provided additional safety data to allow inclusion of patients with baseline platelet counts <75,000/ µl.

Safety and efficacy data obtained from ongoing clinical trials provide additional information regarding the efficacy and safety of INC424 in patients with platelet counts between 50 000 and 75 000/µl, with a level of efficacy comparable to what is observed in patients with higher platelet counts and comparable safety profile (Harrison 2012, Talpaz 2012). In these studies, patients with lower baseline platelet counts were initially treated with ruxolitinib 5 mg p.o. BID. Patients with lower platelet counts may be treated as per marketing authorization in countries where INC424 is approved by the local Health Authority. In order to address treatment needs in this population in countries where INC424 is not yet available, and to gather additional safety and efficacy data, the trial recruitment is extended to patients having a baseline platelet count between 50,000 and 75,000/ µL.

There continues to be a high level of unmet clinical need among patients with MF in countries where the local regulatory approval and commercial availability of INC424 has not yet been granted.

Due to previous consideration, an amendment is deemed necessary to extend recruitment duration and allow additional patients to be recruited until treatment is deemed available.

The major changes to the protocol include:

1.0 Addition of inclusion criteria for patients having a 50,000 to 75,000/ µL baseline platelet count if all other inclusion/exclusion criteria are met, and addition of dosing instructions for those patients for an initial dose of 5 mg p.o. BID.

2.0 The sample size is to be increased up to a maximum of 2484.

3.0 Enrollment to the study will complete when the maximum number of patients has been enrolled or December 31, 2014, whichever comes first.

4.0 The decision regarding end of treatment will now include physician decision.

5.0 Data analysis will no longer be performed annually, but may be performed if needed to fulfill regulatory request or publication purpose.

6.0 Where Country-specific local Health Authority approval is in process, drug supply is updated to take into account that drug may be supplied centrally, or locally if deemed necessary after local Health Authority approval have been granted.

7.0 Statistical analysis reflecting updates in estimated end of enrollment and end of treatment, with inclusion of patients with baseline platelet count of 50,000 to 75,000/µL in the pool of patients with low platelet counts.

8.0 Update AE definition and processing.

[redacted]

9.0 Update reference list

## Study Status

The trial is currently enrolling and close to reaching the original estimate of 1600 patients.

**Changes to the Protocol**

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

a. Study Synopsis
   - Background
     - Update on regulatory approvals obtained from 2012 in several countries.
     - Updated clinical trial data (Expand) (Harrison 2012) and addition of data from a Phase II trial in patients with low baseline platelet counts (Talpaz 2012)

b. Endpoints (safety)
   - Clarification regarding laboratory value analysis.

c. Endpoints (efficacy)
   - Clarification regarding platelet and WBC analysis.

d. Study design
   - Deletion of planned 2 year duration of recruitment period and insertion that enrollment to the study is estimated to complete when the maximum enrollment of 2484 patients is reached or December 31, 2014, whichever comes first.

e. Sample size
   - Deletion of 1600 plus a 20% attrition rate as projected number of patients to be treated in the study and insertion of a maximum of 2484 patients to be enrolled.

f. Inclusion, exclusion criteria
   - Inclusion/exclusion criteria: exclusion criteria 9 is updated to reflect possible inclusion of patient with a 50,000/ µL platelet count at minimum based on additional data obtained from clinical trial and to allow inclusion of patients having the same health state that the ones authorized to receive treatment as per marketing authorization in the Europe.

g. Dose, regimen, treatment
   - Updated starting dose instructions taking into account patients enrolled with a 50,000/ µL platelet count. Based on available efficacy and safety data and to reflect recommended dose as per marketing authorization, the starting dose for those patients will be 5 mg p.o. BID. Patients with platelet count below 50,000/ µL are ineligible for this trial.
     For those patients who start INC424 treatment at a dose of 5 mg p.o. BID, dose increases can be made, at the discretion of the investigator, as described below. The dose of INC424 may be escalated 5 mg once a day starting at week 4, and thereafter, no more than once every two weeks ONLY if:
   - The patient must not have had a prior safety-related dose reduction.

[redacted]

- Platelet count remains ≥ 50,000/μL since last lab scheduled visit.
- ANC > 1000/μL since last scheduled visit.
- No dose reduction or interruption for safety occurred in the preceding weeks after the last planned visit.
- The dose increase may only be an increase of 5 mg o.d. i.e., from 5 mg PO BID to 5 mg QAM and 10 mg QPM.
- The total dose may never exceed 25 mg BID.
  Following a dose increase, platelet count and ANC levels should be assessed approximately 2 weeks after the dose adjustment. If a regularly scheduled Study Visit does not coincide with this required blood draw, an unscheduled Interim Visit should be held to collect samples for hematology.
  Dose interruptions of dose reductions for patients starting INC424 5 mg BID are made according to the platelet counts:
  - If platelets ≤25,000/ μL and/or ANC <500/ μL, treatment is to be held
  - If platelets >25,000 to <50,000/ μL, INC424 dose will be reduced by 5 mg o.d.
- The patient should then be reassessed the following month. If the platelet count improves, the patient can restart treatment, and if the platelet count does not improve, the patient should be withdrawn from the study.
- Add physician decision to reasons for end of treatment

h. Supply, preparation, and administration
   - Addition of statement that INC424 may be supplied centrally or locally by Novartis and that storage condition can refer to local or study label

i. Statistical methods and data analysis
   - Clarification regarding laboratory values analysis

j. Interim Analysis
   - Deletion of description of analyses to be performed annually beginning with a data cutoff of December 2012 and insertion of statement that analyses may be performed as needed to fulfill regulatory request or for publication purposes.

k. Section 1.3.4 INC424 clinical safety and efficacy in phase I/II trials
   - Update from data presented at the American Society of Hematology meeting in December 2012 (Harrison 2012)
   - Additional clinical trial data from a phase II study presented at the American Society of Hematology meeting in December 2012 (Talpaz 2012)

l. Section 2.2 Rationale for dose and regimen selected
   - Updated with clinical trial data (Harrison 2012, Talpaz 2012)

m. Section 3.3 Study Endpoint
   - Clarification of laboratory value analysis
   - Clarification of platelet and WBC analysis

n. Section 4.1 Description of study design
   - Insertion of estimation that enrollment will complete when the maximum enrollment of 2484 patients is reached or by December 31,2014, whichever comes first

[redacted]

- Insertion of physician decision as a reason for end of treatment

o. Section 5.3, Exclusion criteria.
- Exclusion criteria 9 is updated to reflect possible inclusion of patient with a 50,000/µL platelet count at minimum based on additional data obtained from clinical trial and to allow inclusion of patients having the same health state that the ones authorized to receive treatment as per marketing authorization in the Europe.

p. Section 6.1.1 Study drug dosing
- Update dosing instructions
  - Dosing instructions are updated to take into account patient enrolled with a 50 000/µl platelet count. Dosage combination table is also updated accordingly.
- Addition of physician decision as a reason for end of treatment

q. Section 6.5.1 Study drug preparation and dispensation
- Addition of physician decision as a reason for end of treatment

r. Section 6.5.2 Study drug packaging and labeling
- Addition of physician decision as a reason for end of treatment

s. Section 6.5.3 Drug supply and storage
- Table 5-6: addition of statement that INC424 may be supplied centrally or locally by Novartis and that storage condition can refer to local or study label

t. Section 7.2.1 Efficacy
- Updated estimated end of recruitment when the maximum enrollment of 2484 patients is reached of December 31, 2014, whichever comes first.

u. Section 7.5.1.9 Week 24 (± 7 days)
- Deletion of collection of Medical Resource Utilization (MRU) in the past 3 months to correct MRU collection in the past month,

v. Section 7.6.1 Criteria for premature withdrawal.
- Adjustment to reflect acceptable lower limit for baseline platelet count of 50,000/µL.

w. Section 9.1.1 AE Definition and Reporting
- Update on AE definition and processing.

x. Section 11 Statistical methods and data analysis
- Timing of analyses
  - Deletion of description of analyses to be performed annually beginning with a data cutoff in December 2012 and insertion of statement that analyses may be performed as needed to fulfill regulatory request or for publication purpose.
  - Change in analysis to data will be analyzed according to platelet count at baseline
- Statistical reporting and grouping
  - Update of definition of baseline value to integrate that if a baseline assessment is not available prior to the start of first dose, assessment on the day of first dose may be used as baseline.

y. Section 11.3 Patient demographics/other baseline characteristics

[redacted]

- Change from analysis based on summary of patients in safety set to summary based on FAS

z. Section 11.4 Treatments (study drug, concomitant therapies, compliance)
- Deletion of summary of duration of dose interruptions

aa. Section 11.5 Primary objective
- Deletion of death for consistency with Section 3.1

bb. Section 11.5.1 Variables
- Deletion of analysis of incidence of AEs by patient and statement "(i.e., incidence) considering or not certain AE characteristics (e.g., relationship to study medication severity)
- Clarification of incidence to "ratio of the total number of patients experiencing at least one AE (defined by its preferred term) divided by the total number of patients in the safety set"

cc. Section 11.5.2 Statistical hypothesis, model, and method of analysis
- Removal of analysis of deaths and death rate since death is not part of the primary analysis

dd. Section 11.6 Secondary objectives; Section 11.6.1 Variables
- Clarification of the definitions of progression free survival, leukemia free survival, and overall survival

ee. Section 11.6.1.2 Statistical hypothesis, model, and method of analysis
- Clarification of the summary of WBC and platelet count changes as descriptive statistics

ff. Section 11.6.3 Other safety data
- Descriptive statistics for ECGs have been deleted and replaced by "Notably abnormal changes in ECG parameters will be displayed in listings" in amendment 02. Previous description which is no longer applicable regarding Descriptive analysis of ECGs parameters did nevertheless remain, which is corrected.
- Addition of assessments of deaths and death rate (moved from Section 11.5)

gg. Section 11.6.5 Quality of Life Assessments.
- CINC424A2414 Quality of Life analyses consist of visits and not of cycle. Wording have been corrected regarding Quality of Life data analysis to clarify that analysis will be based on visits.

hh. Section 11.7 Interim analysis
- Deletion of description of analyses to be performed annually beginning with a data cutoff in December 2012 and insertion of statement that analyses may be performed if needed to fulfill regulatory request or publication purpose.
- Update IA for patients with low platelet count
- Include patients with platelet count between 50,000 and 99,000 / IU in this population

ii. Section 11.8 Sample size calculation
- Deletion of 1600 plus 20% attrition rate as projected number of patients to be treated in the study and insertion of a maximum of up to 2484 patients.

[redacted]

jj. Section 13 References
- Updated reference list with additional references (Harrison 2012, Talpaz 2012)

## Amendment 2

## Amendment rationale

Since the FPFV date in the JUMP trial our understanding of INC424 in the treatment of MPN has changed and thus revisions to the protocol are necessary to adapt to these new findings.

The major changes to the protocol include:

1. To re-evaluate the inclusion and exclusion criteria to the study:
   - New safety data from [CINC424A2352], [INCB 1824-351], and the [CINC424A2201] trials provided further information on the safety of treating patients with low platelet values with INC424. Therefore some inclusion and exclusion criteria are no longer necessary.
   - Modification of the inclusion criteria to include patients with platelet counts between 75,000 and 99,000/μL
     a. Per epidemiology data (Mesa et al 2007), 16.5% of all MF patients are reported to have platelet counts < 100,000/μL 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
     b. Data from ongoing trials presented at medical congresses in 2012 (Gisslinger 2012, Talpaz 2012) have revealed that INC424 can be safely administered in patients with platelet counts between 50,000/μL and 99,000/μL, producing a level of efficacy comparable to what is observed in patients with a higher platelet count.
     c. The protocol has been updated with references to this data, and also to broaden the inclusion criteria to include patients with platelet counts between 75,000 and 99,000/μL. This patient population represents 25% to 30% of total MF patients, and by including them, we will increase the possibility to cover the global medical need in MF.
     d. The dose of INC424 in patients with platelet counts between 75,000/μL and 99,000/μL differs from patient with platelet counts ≥ 100,000/μL. In order to provide more clarity on how to administer INC424 in this group of patients, the protocol has been amended to provide a detailed description of how to start and how to adjust the dose based on response and platelet counts.
     e. Fluctuation in the platelet counts inherent to the nature of the disease has precluded potential patients' qualification in the study. Therefore the qualifying platelet criteria have been revised.
2. Increase the enrollment sample size from 950 to 1600 patients plus a 20% attrition rate
   - In addition to enrolling more patients due to the broader inclusion/exclusion criteria (i.e., inclusion of patients with low platelets), there is a need to address the increased medical need of patients with MF at the country level. This resulted in a reassessment of trial commitments by countries for target patient enrollment, and led to an increased

[redacted]

estimation of approximately 1600 patients plus a 20% attrition rate enrolled by the end of trial.

3. Addition of interim analyses
   - With the enrollment of a larger sample size and the inclusion of patients with a baseline platelet count between 75,000 and 99,000/μL, an interim analysis is introduced when 50 patients with a low baseline platelet count have received at least 6 months of therapy. This analysis is intended to provide preliminary information on safety and efficacy on patients with a low platelet count in comparison with the patients who started with a higher platelet count (≥100,000/μL),
   - Analyses will also be performed annually, beginning with a data cutoff in December 2012. These analyses will include descriptive summaries of demographic and baseline characteristics, disposition, spleen length response and adverse events. These analyses will primarily be used for publication purposes.

## Study Status

The trial is currently enrolling and approaching the original estimated accrual of 950 patients.

## 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 and bold for insertions.

- Updated author list of protocol [redacted] to reflect the team currently working on/managing the protocol
- Updated the table of contents to reflect changes made to the protocol; modified table numbers; modified the number of appendices following removal of Appendix II
- Updated the glossary of terms: the medication number has been deleted from both the glossary of terms and Section 6.5.2, as it is not applicable to this study; the patient number will be the only identifier used and included on the drug dispensing label for this particular study. The glossary of terms for 'patient number' has been updated to reflect the inclusion of this identifier on the drug dispensing label.
- Delete references to overnight fasting of at least 8 hours or since midnight as no pharmacokinetic studies are being performed
  - There is no need to collect fasting blood specimen
- Update the list of abbreviations to include all abbreviations used in the protocol as several were missing from the original version of the protocol
- Delete IRT and any references to it throughout the protocol, as this was not used in this protocol
- Add INR to coagulation parameters as an option for those institutions who are unable to measure PT/PTT (not mandatory for all regions, only those regions who are unable to perform PT/PTT estimations)
  - Not all countries enrolling patients are able to measure a PT/PTT, and can measure INRs, and as such INR was added to reflect current methods of assessing coagulation status in certain countries

[redacted]

- Ensure consistency of language throughout the protocol where set abbreviations are used e.g. FACT-Lym version 4
- Change spleen size to spleen length in body of protocol (not changed in the background section to ensure consistency with published information): spleen length is a more accurate assessment of response to treatment and provides a more uniform assessment across the conduct of the study (compared to ultrasound and MRI)
- Glossary of terms: changed the definition of medication number as this not a randomized trial and does not apply. It is a correction from the original protocol.
- Removal of reference throughout to "cycle". INC424 is administered continuously, thus cycle terminology does not apply
- Clarified throughout that additional bone marrow biopsies are not mandatory as the endpoints of the trial are assessment of best overall response, which is characterized by the percentage change in spleen length compared with baseline, observed during the study follow-up period
    - Deleted Appendix II as this pertains to traditional measures of disease response; as a consequence renumber Appendix II – X (will not become I – IX in total)
    - All references to Appendix II – X were updated with new numbering throughout the protocol
- Change the requirement of bone marrow biopsy to be performed at the discretion of the investigator and not as a timed procedure. Bone marrow examinations are performed as a tool for diagnostic purposes in MF but are not a standard requirement for the management of the disease, which is largely based on physical examination. A bone marrow biopsy may also be performed as a routine part of clinical care when determining progression to acute leukemia, based on alterations to peripheral blood counts.
- Study synopsis
    - Background updated to include:
        - Inclusion of the New England Journal of Medicine Phase III data on safety and efficacy of INC424 (Verstovsek 2012 and Harrison 2012) as the data were not published at the time the protocol was written
        - FDA approval date as this occurred since the original protocol was released
        - Detailed description of the COMFORT-I and COMFORT-II trials (safety and efficacy) as they are now published in peer reviewed journals
        - Safety and efficacy data supporting dosing of INC424 in patients with platelet counts between 75,000/µL and 99,000/µL as the inclusion criteria have been expanded to include this group of patients
    - Purpose/rationale: added the FDA approval date; added in data cut-off dates for COMFORT-I and COMFORT-II as data newly available
    - Endpoints (safety, quality of life): changed language in medical resource utilization to include frequency of general practitioner, specialist, urgent care, and emergency room visits (changed throughout protocol)
    - Endpoints (efficacy): clarified how data will be collected and presented

[redacted]

- Changes in spleen length and WBC/platelet count changes from baseline to each visit (no longer per cycle/month). INC424 is administered continuously therefore there is no cycle.
- Where bone marrow biopsy data are available, changes in fibrosis from baseline to the worst value will be reported (NOTE: biopsies are not mandatory) (Appendix V)

- Study design:
  a. Changed period in which baseline evaluations should be performed from 2 weeks to within 1 week of the first dose of INC424: modified to correlate with Table 7-1 (Day -7 to Day -1); was a typographical error in the original protocol
- Population:
  - Added in danocrine (Danazol®) as a permitted prior treatment

    Many countries use danocrine (Danazol®) and the lack of a mention of the agent in the protocol resulted in a number of calls to the study monitors and hence required clarification
  - Clarified the time period in which all prior treatment for PMF, PPV MF, or PET-MF must be discontinued prior to the initiation of INC424

    The lack of clarification of the time in which prior therapy should be discontinued resulted in a significant number of queries and confusion from study sites; thus provided clarification

  a. Specified countries that are participating in the JUMP trial
- Sample size:
  - Increase the enrollment sample size from 950 to at least 1600 patients plus a 20% attrition rate
  - In addition to enrolling more patients due to the broader inclusion/exclusion criteria (i.e., inclusion of patients with low platelets), there is a need to address the increased medical need of patients with MPN at the country level. This resulted in a reassessment of trial commitments by countries for target patient enrollment, and led to an increased estimation of approximately 1600 patients plus a 20% attrition rate enrolled by the end of trial.
- Inclusion criteria:
  a. Clarified the timing of risk assessment to the screening visit as it was not listed in the original protocol
  b. Added in direct bilirubin exclusion limits
  - Added total bilirubin as the initial value to be estimated where direct bilirubin assessments are not standard (and exclusion limits).

    It is local practice, for some countries, to perform an initial assessment of total bilirubin. When elevations in the total bilirubin are documented, separation by direct and indirect bilirubin will occur.
- Exclusion criteria:

[redacted]

a. Deleted criteria that excludes patients who are receiving hematopoietic growth factors

Data have become available since the original INC424 studies were performed that suggest INC424 can be safely coadministered with hematopoietic growth factors. Deleting these exclusion criteria has the potential to enable greater enrollment.

a. Deleted "patients currently participating in COMFORT-I and the COMFORT-II trial" as the inclusion criteria specifies patients should not be eligible for any other INC424 trial so this criterion is addressed; furthermore these trials are closed to accrual.

The COMFORT-I and COMFORT-II trials are also fully enrolled at this time, so the exclusion criteria no longer applies

a. Clarified that the definition of inadequate bone marrow reserve pertains to the baseline visit and also modified the lower platelet threshold (as the new dosing cohort was added)

Modified the requisite baseline platelet count to 75,000/μL, from 100,000/μL, based on the inclusion of the new cohort of patients with thrombocytopenia who start INC424 dosing at 5 mg BID when platelets are between 75,000/μL and 99,000/μL

a. Add in INR > 1.5 x ULN to laboratory parameters

Previous version of the protocol had the incorrect upper limit of normal (0.5); modified protocol to include upper limit of > 1.5 and also to include INR as an option where PT/PTT estimations cannot be performed

- Updated the pregnancy language to be consistent with accepted Novartis documentation for highly effective contraception by the Pharmacovigilance department. These changes are not due to documentation of teratogenic effects of INC424.

a. Patient numbering: changed the time from 2 weeks to 1 week for starting treatment from time of meeting eligibility criteria.

This was to correct the erroneous variable on the original protocol; was supposed to be 7 days when the trial was initiated.

- Investigational and control drugs: added in that there is no control drug in this study as it is an open-label study

- Dose, regimen, treatment cycle:
  a. Added in a category of patients with platelet counts between 75,000 and 99,000/μL to be dosed at 5 mg BID INC424
  b. Added in details for the patient population above regarding dose modifications (increases and decreases/interruptions)

[redacted]

c. Clarified the dose escalation requirements that were originally listed in the protocol pertain to the 15 – 20 mg BID cohort only

- MRU: clarified the visits that will be captured are to include emergency room visits, urgent care visits, general practitioner and specialist visits, in addition to splenectomy/splenic irradiation, transfusions, and concurrent medications
- Efficacy assessments: clarified how patients who are splenectomized will be monitored
  a. This group of patients is being enrolled onto the study, and the efficacy endpoint of changes in spleen length is not assessable in the splenectomized patients. As such efficacy outcomes will be based on patient reported outcomes only in this population
- Statistical analysis updated to include:
  a. The primary analysis will be performed after all patients have either completed 24 months of treatment or have been prematurely discontinued from the study. All patients should have been followed for 28 days after they have discontinued INC424. Data collected during this follow-up period will be included in the analysis.
  a. Statistical reporting and grouping
  Data will be analyzed according to platelet count and displayed considering the following two groups:

  (a) Low platelet patients (platelets < 100,000 /μL)
  (b) Non-low platelets (platelets ≥ 100,000 /μL)
- Interim analysis
  a. The interim analysis planned for this study will take place when 50 patients with low platelets have completed 6 months of treatment
  b. Interim analysis will be performed annually, beginning with a data cutoff in December 2012.

- Section 1 (background): added detail on FDA approval in the USA, including date of approval and indication
- Section 1.3.4.2: Added data from the Phase 1b study of INC424 in patients with MF and baseline platelet counts between 50,000 and ≤ 99,000/μL to justify inclusion of patients with lower platelet counts
  a. Resulted in the renumbering of items in this section

a. Section 1.3.5 (phase 3 studies): updated to include data from recently published Phase 3 trials (COMFORT-I and COMFORT-II); added description of the 2 trials; outline efficacy and safety results from the licensing studies; updated safety information from the IB
b. Section 2.1 (study rationale and purpose): updated to include published COMFORT-I and COMFORT-II safety and efficacy data
c. Section 2.2 (rationale for dose and regimen): added data to support inclusion of patients with platelet counts between 75,000 and 99,000/μL
d. Section 3.3.2 (study endpoints, efficacy): change mention of cycle to visits; change in fibrosis to shift in fibrosis; provided clarification that bone marrow biopsies on study are

[redacted]

not mandatory; added in assessment of efficacy in patients who are splenectomized; clarified best overall response (as outlined in synopsis changes)

e. Section 3.3.4 (Study endpoints, MRU): updated to include general practitioner, specialist, and urgent care visits in addition to emergency room visits (as outlined in synopsis changes)

f. Section 4.1 (study design):
   a. Removed description of cycles, as INC424 is administered continuously (provided no AEs)
   b. Described the ability to use historical results (if within protocol requirements) during the 28 days prior to Day 1 to avoid duplication when the screening and baseline visits are combined on the same visit
      a. Clarification that laboratory assessments and other examinations performed consistent with protocol requirements within a week of the first dose of INC424 are able to be used , and that duplication of results in this setting is not necessary
   c. Provided details on the FPFV and the planned recruitment period:
      1. The FPFV occurred on 16 August 2011 and the recruitment period is planned to last 2 years.
   d. Added patients are able to be rescreened if they fail an initial study screening at the discretion of the investigator, but no more often than every 7 days
   e. Clarified that the treatment of patients in the treatment period is contingent of meeting study criteria

g. Figure 4-1: remove mention of cycles; change to continuous dosing; replaced figure with a more descriptive image to describe what is occurring on study

h. Section 5.2 (Inclusion criteria):
   a. Provided additional references for diagnosis of PMF, PPV MF, and PET-MF as not encompassed in original reference (Appendix I)
   b. Clarified the need to determine patient risk at the screening visit
   c. Clarified the 5 prognostic factors as defined by Cervantes (old version had merged criteria)
   d. Added total bilirubin as a determinant of liver function test abnormalities
      - It is local practice, for some countries, to perform an initial assessment of total bilirubin. When elevations in the total bilirubin are documented, separation by direct and indirect bilirubin will occur.

i. Section 5.3 (Exclusion criteria):
   3 Delete exclusion of patients participating on the COMFORT-I trial as this trial is now completed
   4 Delete exclusion criteria of “patients undergoing treatment with hematopoietic growth factor receptor agonists” as there are data available demonstrating safety when coadministering INC424 with hematopoietic growth factor receptor agonists (Gisslinger)
      - Concomitant ESA and INC424 use does not appear to affect these reductions in spleen size

[redacted]

- No substantially different AEs were reported in patients receiving INC424 in combination with ESAs compared with INC424 alone

5 Update coagulation parameters to also include INR (optional) as not all institutions are able to determine PT/PTT. Assessment of coagulation and response to anticoagulants can effectively be evaluated using INR where PT/PTT estimations are not able to be performed [(PT, PTT, INR) > 1.5 x ULN] i.e., either PT/PTT or INR

6 Updated the definition of inadequate bone marrow reserve to enable patients with platelet counts between 75,000/μL and 99,000/μL to be enrolled

7 Updated child-bearing criteria to include "highly effective contraception" according to Novartis Standards. These changes are not being made because of teratogenic risk, rather to be consistent with the verbiage provided by Novartis Pharmacovigilance.

j. Section 6.1.1 (study drug dosing):
- Moved information on supply of study drug to this section
- Removed reference to "cycles" as the study drug is administered continuously
- Added in the third cohort of dosing of 5 mg p.o. BID for patients with baseline platelet counts of 75,000/μL – 99,000/μL
- Standardized units of reporting of platelets to thousand/μL, and not x $10^9$/L

k. Section 6.1.2 (treatment duration): deleted this section from the protocol as there is no defined treatment period in this program/study other than it is continues until one of the stop marker hit. And these stop markers are already described in 6.1.1.

l. Section 6.2.1 (dose increases after Week 4 [Month 1]):
   a. Modified the section to make reading of dose modifications more clear. Separated into dose increases for patients starting at a dose of 15 – 20 mg BID (6.2.1.1) addressing dose increases after week 4 and then separately after week 4; then added section 6.2.1.2 for patients starting at a dose of 5 mg BID, similarly addressing dose increases after week 4 and then separately after week 4
   b. Modified the section to include permissible Week 4 (and beyond) dose increases for those patients who start the study with platelets between 75,000 – 99,000/μL
   c. Modified the section to include permissible dose increases beyond week 4 to include modifications for patients with platelet counts between 75,000 – 99,000/μL

m. Figure 6-1: replaced the figure with a clearer image

n. Section 6.2.2 (dose interruption or dose reduction): modified this section to include dose interruption/dose reduction schedules to encompass the new cohort of patients with platelet counts between 75,000 – 99,000/μL

o. Table 6-2: clarified that this table only applies to patients who start on INC424 doses of 15 – 20 mg p.o. BID

p. Added Table 6-3 to address the dose reduction strategy for patients with platelet declines in patients with platelet counts between 75,000 – 99,000/μL at the start of therapy

q. Section 6.2.2.3: Added dose modifications for renal impairment as data now available in the IB and these data were not available at the time the original protocol was written

r. Section 6.2.2.4: Added dose modifications for hepatic impairment as data now available in the IB and these data were not available at the time the original protocol was written

[redacted]

s. Section 6.2.3 (restarting or reinstituting previous dose for patients who start INC424 15- 20 mg BID)

1. Clarified that the details contained within this section apply only to patients who started INC424 at a dose of 15 – 20 mg BID
2. Eliminate the requirement for a maximum dose of INC424 to be 5mg BID less than the dose which caused a platelet count reduction < 100,000/µL. Restricting the dose to no higher than 5 mg BID less than any dose that caused a platelet count < 100,000/µL has limited the capacity of physician-investigators to dose patients higher when their platelet counts have improved above 100,000/µL, sometimes even to within normal range.

t. Section 6.3.2 (permitted concomitant therapy requiring caution and/or action):

1. Removed the exclusion of corticosteroid therapy
   1. Corticosteroids were not permitted in the phase III trials, because they could induce a response in the constitutional symptoms of MF, making it difficult to assess the real impact of INC424. As this is not a randomized trial, steroids are permitted.
2. Added in need for dose modification of INC424 in the presence of dual CYP2C9 and CYP3A4 inhibitors such as fluconazole to comply with some counties' SMPC
3. Added in detail regarding preferred anticoagulation if needed as follows: If anticoagulation is required during INC424 administration, low molecular weight heparin is preferred, particularly in patients who are: elderly, history of CHF, diabetic, hepatic or renal disease, or atrial fibrillation (first episode).
4. Removed the limitation on hematopoietic growth factors (see earlier explanation)

u. Section 6.3.3 (Prohibited concomitant therapy):

1. Clarified the time period in which prior treatment for the management of PMF, PPV MF, and PET-MF should be discontinued prior to administration of INC424
2. Corticosteroid therapy is no longer prohibited
   1. Corticosteroids were not permitted in the phase III trials, because they could induce response in some of the constitutional symptoms of MF, making it difficult to assess the real impact of INC424. As this is not a randomized trial, steroids are permitted

v. Section 6.4.1 (patient numbering): remove discussion on randomization as this is an open-label study and does not apply

w. Section 6.4.2 (treatment assignment and randomization): clarified that this is not a randomized trial and as such no randomization will occur

x. Section 6.5.2: The medication number has been deleted from both the glossary of terms and Section 6.5.2, as it is not applicable to this study; the patient number will be the only identifier used and included on the drug dispensing label for this particular. The glossary of terms for 'patient number' has been updated to reflect the inclusion of this identifier on the drug dispensing label.

y. Table 7-1:

1. Updated to hyperlink to pertinent sections in the protocol such as end of study treatment, to enable easier cross-referencing within the protocol for the end-user
2. Added in disease status documentation to be performed at baseline

[redacted]

3. Added in bone marrow biopsy requirement (at baseline only for diagnostic purposes), but not mandatory following diagnosis. Additional bone marrow biopsies will only performed at the discretion of the treating physician as part of routine care and are not required for the protocol.
4. Added in assessment points for BM fibrosis (not mandatory) but when performed needs to be collected in a standardized time point
5. Added in assessment point for leukemia-free survival

z. Table 7-2:

1. Updated to hyperlink to pertinent sections in the protocol and added in the ability to check the INR for those institutions where PT/PTT measurements are not feasible

aa. Section 7.2.1 (efficacy): clarified that assessments at baseline are for disease status only, not response to treatment as patients will not be receiving INC424 at this time; all future visits will evaluate response to INC424 treatment

bb. Section 7.3 (screening):

1. Blood sampling for hepatitis updated to include all requisite tests including Hepatitis A (IgM antibody); Hepatitis B (Hepatitis B surface antigen [HBsAg], Hepatitis B surface antibody [HBsAb], Hepatitis B IgM core antibody [HBcAb-IgM]; and Hepatitis C (Hepatitis C antibodies [HC Ab]) or local health authority requirements
2. Added the need to specify risk group of patient at screening visit

cc. Section 7.4 (baseline evaluations):

1. Removed requirement to fast prior to baseline evaluation
2. Update MRU information collection (see synopsis)
3. Removed the need to fast prior to baseline evaluations

dd. Section 7.4.1: added to address actions to be taken when the screening and baseline visits overlap

ee. Section 7.5.1.3 (week 4), 7.5.1.5 (week 8), 7.5.1.7 (week 12), 7.5.1.9 (week 24), 7.5.1.11 (week 36), 7.5.1.13 (week 48):

1. Update MRU information collection (see synopsis) throughout
2. Week 4: modified dose escalation based on starting dose of INC424

ff. Section 7.5.1.16: added in recommendations for management of missed/moved visits

gg. Section 8.1: clarified that the body mass index will be calculated automatically based on collected height and weight

hh. Section 8.2.7 (ECG analysis and reporting): delete the requirement for ECGs to be reviewed by a cardiologist

1. The need for cardiologist-read ECGs is not supported based on the results of the Healthy Volunteer Study (Incyte study 138), and also to date no cardiac concerns have been noted in ongoing trials. Given the importance of monitoring electrocardiographic function with new compounds, however, it will be required to continue obtaining periodic ECG's but the readings may be performed by the treating physician

ii. Section 8.2.8 (clinical safety laboratory assessments): remove the requirement for patients to fast; add in total bilirubin to laboratory values as an alternative for direct bilirubin

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1. Local clinical practices often dictate total bilirubin is evaluated first. If results are within acceptable range then no further testing is required. However, if the total bilirubin result is out of normal range a determination of direct and indirect bilirubin will occur. Modification to include total bilirubin will enable countries to determine if there is an elevation first, before performing additional testing.

jj. Section 8.2.8.1 (pregnancy test): clarified the time period in which the pregnancy test should be obtained i.e., within 14 days of receiving the first dose of INC424

kk. Section 8.3.2.1 (FACT-Lym): removed all references to the FACT-G scale as this is not being used in this study

ll. Section 8.3.2.2 (original protocol): delete all references to FACT-G and section on FACT-G

mm. Section 9.1.1.2 (surgical events related to disease under study): added this section as a separate item. It was incorrectly listed in original protocol under 9.1.2.1 which did not pertain to surgical management.

nn. Section 9.1.2.1 (definition and reporting): deleted references to surgical management creating a separate section (see 53 above) that addresses this need

oo. Section 9.2.2 (reporting): clarified that the reporting period of 28 days (not 30 days) to ensure consistency throughout the protocol

pp. Section 11:

1. Updated statistical methods and analysis to include an interim analysis, including timing of analyses, and statistical reporting and grouping as previously described

qq. Section 11.1 (handling of missing values): updated per BIOS

rr. Section 11.4 (treatments): updated per BIOS to align with the RAP

ss. Section 11.6.1.1:

1. Clarified the change in fibrosis to shift in fibrosis
2. Added in the definition of leukemia-free survival

tt. Section 11.6.1.2 (statistical hypothesis, model, and method of analysis): updated per BIOS

uu. Section 11.6.2.2: added in a subsection for biochemistry estimations and presentation/analysis of data

vv. Section 11.6.3: added in verbiage to address reporting of ECG and blood pressure results

ww. Section 11.6.4.1 (resource utilization): clarified data to be presented in the RAP

xx. Section 11.7: added details surrounding the interim analysis to be performed and consistent with the rest of the protocol

yy. Section 11.8: deleted text on INC424 procurement as it does not relate to sample size calculation; added in rationale for new sample size calculation (see earlier in rationale)

zz. References: added in new references (Verstovsek NEJM 2012; Harrison 2012, Swerdlow 2008; Gisslinger 2012; McMullin 2012, Mesa 2007, Talpaz 2012), and deleted non-pertinent references (Trussell)

aaa. Appendix I: added in criteria for diagnosis of PPV MF and PET-MF (Barosi) as they were not in the protocol previously

bbb. Appendix II: deleted (see earlier in rationale)

[redacted]

ccc. Appendix III (now II): deleted old appendix and inserted Novartis standard language for highly effective contraception per Pharmacovigilance

ddd. Appendix IV (now III): added in direct bilirubin, INR (where PT/PTT not feasible); alkaline phosphatase (where feasible); outlined hepatitis panel to be evaluated

eee. Appendix X (now IX): removed agents that are contraindicated in the protocol from the concomitant medication list

### IRB/IEC

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

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

## Amendment 1

### Amendment rationale

2. The protocol version 00, dated 25-Jan-2011, contained some inconsistencies that required correction, thus Amendment 1 was prepared to address these issues.
3. These inconsistencies included:
   a. Clinical study protocol synopsis: exclusion criteria number 13: patients with coagulation parameters (PT, PTT, INR) >5 x ULN should be corrected to read >1.5 x ULN which is the correct coagulation parameters and the omission on page 15 is considered a typographical error.
   b. Study design: screening window: figure 4-1: -14 to -1 Day of screening and eligibility clearly noting it should be up to 28 days before first dose; the typographical error was corrected.
   c. The correct days before first dose should be “up to 28 days before first dose” as written in the text of the protocol under screening and eligibility.
4. There are strict internal policies that govern the development of a protocol and the process in which it undergoes final internal review and approval. Upon final approval and sign-off by the appropriate reviewers, the process mandates that version control is achieved through one of our specified internal electronic systems. Only the version available in the electronic system is the approved protocol and related study documents.
   a. Due to a human error, an unapproved version of the amendment 01 dated 05 May 2011 was released and submitted to Health Authorities in 12 countries.
   b. This error was discovered and all affected Health Authorities were informed. This erroneous amendment 01 version was retrieved. Sites were asked not to use this version and informed that an amendment 02 would be prepared to address the above mentioned errors.

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## IRB/IEC

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

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

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## Oncology clinical study protocol synopsis

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| **Investigational drug** | INC424 (ruxolitinib) |
| **Protocol no.** | CINC424A2401 |
| **Study phase** | IIIB |
| **Study title** | An open-label, multicenter, expanded access study of INC424 for patients with primary myelofibrosis (PMF) or post-polycythemia vera myelofibrosis (PPV MF) or post-essential thrombocythemia myelofibrosis (PET-MF). |
| **Study population** | Male or female patients ≥ 18 years of age who have been diagnosed with PMF, PPV MF, or post-essential thrombocythemia myelofibrosis (PET-MF) (Appendix I), who meet intermediate-1 criteria and have palpable splenomegaly of at least 5 cm below the costal margin, or who meet intermediate-2 criteria, or who meet high-risk prognostic criteria. Patients are not required to have received prior therapy for MF. |
| **Study objectives** | **Primary objective**<br>- To collect additional safety of INC424 in patients with PMF, PPV MF, or PET-MF, who have either received prior treatment with commercially available agents, investigational drug, or never received treatment.<br><br>**Secondary objectives**<br>- To assess the best overall response rate of INC424 in patients with PMF, PPV MF, or PET-MF as evaluated by the Investigator.<br><br>- To collect (QoL) information in patients with PMF, PPV MF, or PET-MF treated with INC424.<br><br>- To document MRU in patients with PMF, PPV MF, or PET-MF treated with INC424 |
| **Background** | Myelofibrosis (MF) is a clonal hematologic neoplastic disease characterized by the presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis (Tefferi A (2008)), splenomegaly, anemia, and debilitating constitutional symptoms that include fatigue, weight loss, pruritus, night sweats, fever, and bone, muscle, or abdominal pain (Mesa RA, Niblack J, Wadleigh M, et al (2007), Abdel-Wahab OI, Levine RL (2009)). MF can either be primary in origin (primary myelofibrosis, or PMF) or result from progression of polycythemia vera or essential thrombocythemia vera (Tefferi A (2008)). The median age at diagnosis of MF is approximately 65 years. Patients with myelofibrosis have shortened survival that ranges from a median of approximately 2 years to 11 years depending on the presence of certain risk factors that define their risk category including age, anemia, leukocytosis, etc<br><br>The JAK2V617F mutation has been identified in over 95% of patients with PV and approximately 50% of patients with essential ET and PMF. The JAK2V617F mutation alters the JAK2 tyrosine kinase making it constitutively active. As a result, polycythemia, thrombocythemia and leukocytosis can develop independently from growth factor regulation. Even in patients lacking a confirmed JAK2 mutation, the detection of STAT activation suggests dysregulated JAK activity. Development of JAK1 and JAK2 targeted therapies has the potential to improve the outcome of patients with PMF, PPV MF, and PET-MF.<br><br>INC424 (ruxolitinib, Jakafi®), is an oral JAK 1/JAK 2 inhibitor, was approved by the FDA on November 16, 2011 , and approved by the EMA on 31 August 2012, for the treatment of intermediate or high-risk myelofibrosis , including PMF, PPV MF and PET-MF. INC424 is also approved in Canada, Switzerland and other countries. A number of clinical trials were performed supporting the approval, including Phase I/II trials - completed; Phase III COMFORT-I trial (Verstovsek 2012) and COMFORT-II trials (Harrison 2012) completed, data cut-off 2 Nov 2010 and 4 Jan 2011, respectively. INC424 has demonstrated activity at a range of different doses and dosing intervals ranging from 15 mg - 25 mg BID. The Phase III COMFORT clinical trials evaluated a starting dose of 20 mg BID for patients with platelet counts > 200,000/µL and 15 mg BID for patients with |

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| | platelet counts between 100,000 and 200,000/μL.<br><br>In COMFORT-I (INC424 vs. placebo), significantly more patients in the INC424 arm had reductions in spleen volume (≥35%) which were maintained (67% of the patients with a response had the response for ≥48 weeks). Similarly, significantly more patients had an improvement (≥ 50%) in the total symptom score compared to placebo at 24 weeks (45.9% INC424 vs.5.3% placebo, P<0.001). INC424 was well tolerated in COMFORT-I, with most Grade 3/4 non-hematologic toxicities occurring in less than 6% patients: fatigue 5.2%, diarrhea 1.9%, dyspnea 1.3%, dizziness 0.6%, vomiting 0.6%, arthralgia 1.9%, pyrexia 0.6%, and abdominal pain 2.6%. Hematologic toxicity consisted primarily of anemia and thrombocytopenia. Grade 3/4 anemia occurred in 45.2% patients, and Grade 3/4 thrombocytopenia occurred in 12.9% patients. Approximately half of the Grade 3/4 anemia and thrombocytopenia events occurred during the first 8 weeks of therapy. Treatment with INC424 enabled 41.2% of patients to become transfusion independent. Anemia and thrombocytopenia were manageable, and thrombocytopenia generally responded to dose reduction or temporary dosing interruption. Thirteen deaths occurred in the INC424 group vs. 24 deaths in the placebo group (HR, 0.50; 95% CI, 0.25 to 0.98; P=0.04). The rate of discontinuation of the study drug because of AEs was 11.0% in the INC424 group vs. 10.6% in the placebo group.<br><br>In the COMFORT-II trial (INC424 vs. best available therapy [BAT], 28% of the patients in the INC424 group had ≥35% reduction in spleen volume at week 48 vs. 0% in the BAT group (P<0.001); the corresponding percentages at week 24 were 32% and 0% (P<0.001). The mean palpable spleen length (48 weeks) had decreased by 56% with INC424 but had increased by 4% with BAT. The median duration of response with INC424 was not reached, with 80% of patients still having a response at a median follow-up of 12 months. INC424 treatment was associated with an improvement in overall QOL measures and a reduction in symptoms associated with MF. The most common hematologic abnormalities (≥Grade 3) were thrombocytopenia and anemia. Thrombocytopenia and anemia occurred more frequently in the patients receiving INC424 vs. BAT, a finding that is consistent with the known mechanism of action of INC424, but these events rarely led to treatment discontinuation (one patient in each group discontinued the study owing to thrombocytopenia) and were generally manageable with dose modifications, transfusions of packed red cells, or both. AEs leading to dose modification with INC424 occurred in 41% patients. Only 5% of the patients receiving INC424 required dose interruptions or reductions due to anemia and 1% due to neutropenia. Non-hematologic AEs were rare and mostly grade 1 or 2. Two cases of progression to acute myeloid leukemia were reported with the best available therapy. INC424 was also well tolerated in the COMFORT-II trial, with most Grade 3/4 non-hematologic toxicities occurring in less than 3% patients: diarrhea 1%, asthenia 1%, dyspnea 1%, pyrexia 2%, nausea 1%, arthralgia 1%, fatigue 1%, pain in extremity 1%, abdominal pain 3%, headache 1%, and back pain 2%).<br><br>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, a baseline platelet count of ≥ 100,000/μL has been an inclusion criterion. However, thrombocytopenia is a frequent event in MF; as per epidemiology data (Mesa 2007), 16.5% of all MF patients are reported to have platelet counts < 100,000/μL 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 dose-limiting toxicity of INC424 in MF patients with a maximum tolerated dose of both 25 mg BID and 100 mg o.d. The incidence of grade ≥ 3 thrombocytopenia in this phase I/II trial was 20% at 10 mg BID, 29% at 15 mg BID, and 36% at 25 mg BID. Data from the same trial show that patients who entered the study with baseline platelet counts of 100,000/μL - 150,000/μL 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 BID and 15 mg BID) compared with patients with baseline platelet counts > 150,000/μL, although with a similar nadir (grade 2 and 3). Thrombocytopenia occurred rapidly, and resolved with drug interruptions or dose decreases. In [INCB 18424-251] study, some patients continued to receive INC424 while their platelet count ranged between 50,000/μL |

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| | and 100,000/μL, but no patients with platelet counts below 100,000/μL have initiated INC424 therapy, and therefore the maximum tolerated dose for patients with low platelets needs to be directly established.<br><br>A phase Ib study of INC424 to investigate the safety of INC424 and establish the maximum safe starting dose in patients with MF who have baseline platelet counts ≥ 50,000/μL to 99,000/μL is currently ongoing (Gisslinger 2012). The (Evaluating Ruxolitinib in Patients with Low Baseline Platelet Counts Diagnosed With Myelofibrosis) study is a single-arm, open-label, dose-finding study in adult patients with PMF, PET MF, or PPV-MF. This study consists of two periods: (a) core study period (day 1 to week 24), and (b) an extension period (beyond week 24). There are two different dosing strata based on baseline platelet counts (Stratum 1: 75,000/μL to 99,000/μL; Stratum 2: 50,000/μL to 74,000/μL). An updated analysis was presented at the American Society of Hematology meeting in December 2012. The data (n=20; PMF n=14, PPV=MF n=5, PET-MF n=1) demonstrates that in this phase 1b study of INC424 in thrombocytopenic patients with MF, no DLT has occurred at the first 2 dose levels in patients with platelet counts of 50,000/μL to 99,000/μL. INC424 has been generally well tolerated, similar to the tolerability reported in the previous studies, and no patient has discontinued because of thrombocytopenia. No patient had platelet counts below 20,000/ μL. No Grade 3/4 hemorrhagic events were reported.<br><br>A 24-week, open-label phase II study of INC424 to investigate the efficacy, hematologic effects and dose of INC424 in patients with MF, PPV-MF, and PET-MF and baseline platelet counts of 50,000 to 100,000/ μL is ongoing (INCB018424-258) (Talpaz 2012). The starting dose of INC424 is 5 mg p.o. BID with dose escalation with adequate platelet count by 5 mg once daily every 4 weeks (i.e. 5 mg p.o.AM and 10 mg p.o. PM) to a maximum of 10 mg BID. Further dose escalation requires evidence of suboptimal efficacy. An initial report with data from 41 evaluable patients was presented at the American Society of Hematology meeting in December 2012. Among patients who completed 24 weeks of treatment, most were receiving INC424 dose of 10 mg p.o. BID or higher. No patients have discontinued treatment due to adverse events. Bleeding related events were reported in 7 patients (17.1%). Grade 1 bruising events (contusion n=2 and ecchymosis n=3) were reported in 7 patients. Other bleeding events were reported in 4 patients (subdural hematoma secondary to fall, hematochezia, hemorrhoidal hemorrhage and epistaxis; all grade 1 except grade 2 hematochezia). |
| **Purpose/rationale** | There were no commercially available agents with consistently demonstrated efficacy and safety in PMF, PPV MF, or PET-MF prior to FDA approval of INC424 (INC424; Jakafi®) on 16 November 2011. Based on the results of the Phase I/II trial with INC424, two Phase III trials were initiated and have completed enrollment (COMFORT-I in the USA, Canada and Australia-data cut-off 2 Nov 2010; and COMFORT-II in the European Union). Final results for COMFORT-1 (Verstovsek 2012) showed positive results in the decrease of spleen length. In addition, symptoms associated with these diseases as weight loss, pruritus or fever, were improved with the treatment. This EAP protocol is designed to address an unmet medical need by providing INC424 to patients who are without satisfactory treatment alternatives for PMF, PPV MF and PET-MF, prior to commercial availability at a country level to collect additionally safety data of INC424 in PMF, PPV MF and PET-MF. |
| **Endpoints (safety, quality of life)** | **Safety:**<br>- Safety and tolerability will be collected by monitoring the frequency, duration and severity of all grade AEs by the National Cancer Institute CTCAE v. 3 0, performing physical exams (PE), and evaluating changes in vital signs (VS), ECOG performance status (PS), electrocardiograms (ECGs) and serum chemistry and hematology results.<br><br>- Grade 3 and 4 AEs, Serious Adverse Events (SAEs).<br><br>- Change in laboratory values from Baseline to End of Treatment (serum chemistry and hematology).<br><br>- Changes in weight from Baseline to each assessment point and at end of treatment.<br><br>- Cardiac function as assessed by electrocardiograms (ECGs). |

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| | - Changes in vital signs.<br><br>**Quality of Life** (See Table 7-1 for assessments).<br>- Change in ECOG PS from Baseline to each visit where measured.<br><br>Change in Functional Assessment of Cancer Therapy for patients with Lymphoma (FACT-Lym) version 4 from Baseline to each visit where measured (See Appendix VII).<br><br>- Change in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue from baseline to each visit where measured (See Appendix VIII).<br><br>**Medical resource utilization (MRU)**<br>Medical resource utilization (MRU) will be assessed as follows:<br><br>- Frequency and duration of hospitalization from Baseline up to week 48 of therapy<br><br>- Frequency of emergency room visits from Baseline up to week 48 of therapy.<br><br>- Frequency of general practitioner, specialist, and urgent care visits from Baseline up to week 48 of therapy.<br><br>- Number of transfusions and transfusion dependency status end of study.<br><br>- Splenectomy and use of splenic irradiation.<br><br>- Changes in use of concomitant medications for MPN symptom management (Appendix IX). |
| **Endpoints (efficacy)** | Efficacy data will be collected.<br><br>- Best overall response to treatment as assessed by spleen palpation (calculated as the percentage change in spleen length compared with Baseline).<br><br>- Change in spleen length from Baseline to end of each visit.<br><br>- Change in WBC and platelet count changes from Baseline to end of each visit/month of therapy and at end of treatment.<br><br>- Shift in fibrosis in the bone marrow from Baseline to worst/best value on study (where bone marrow biopsies are performed – not mandatory).<br><br>- Progression free survival, acute myeloid leukemia free survival and overall survival.<br><br>- In patients without splenomegaly, patient reported outcomes measure symptoms of the disease. |
| **Study design** | This is a multicenter, single-arm, open-label expanded access study intended to provide additional data on the safety and efficacy of INC424 in patients with PMF, PPV MF, or PET-MF who have either previously received treatment or have not received treatment. All patients will be screened using inclusion and exclusion criteria (Section 5.2 and Section 5.3) within 28 days prior to the first dose of INC424. See Table 7-1 for a description of the screening evaluations required.<br><br>Baseline evaluations should be performed within 7 days of the first dose of INC424, however platelets should be performed within a maximum of 4 days of the first dose of INC424.<br><br>Subsequently, patients will be asked to visit the clinic monthly for the first 3 months, then every 3 months thereafter, and at study discontinuation.<br><br>All patients will be treated for PMF, PPV MF, or PET-MF in each participating country with |

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| | oral INC424 at a dose of 5 - 25 mg (dose based on Baseline platelet count) BID until either:<br><br>- Disease progression;<br>- Transplant;<br>- Unacceptable toxicity;<br>- Death;<br>- Discontinuation from the study for any other reason;<br>- Withdrawal of consent;<br>- Physician decision;<br>- Until 24-months after LPFV; or<br>- Until the drug is commercially available, whichever occurs first.<br><br>The FPFV occurred on 16 August 2011 and the recruitment period ended on 31 Dec 2014. The study enrolled a total of 2238 patients. The last patient last visit is expected in December 2016. |
| **Population** | Male or female patient's ≥ 18 years of age with a diagnosis of PMF, PPV MF, or PET-MF will be enrolled. Eligible patients who have either never received treatment, or who have received prior treatment with commercially available agents (e.g., busulfan, danocrine [danazol®, hydroxyurea, anagrelide, lenalidomide) or have previously received investigational drug may be enrolled. Patients must meet **all** inclusion and **none** of the exclusion criteria within 4 weeks prior to the first dose of INC424.<br><br>All prior treatment for PMF, PPV MF, or PET-MF must be discontinued prior to Day 1 of INC424, and all AEs attributed to these treatments must be resolved prior to Day 1 of INC424 treatment.<br><br>This study will be conducted worldwide, excluding USA. |
| **Sample Size** | The projected number of patients that will be treated in this study is a maximum of 2500 patients. |
| **Inclusion/exclusion criteria** | **Inclusion Criteria**<br><br>Patients eligible for enrollment in this study have to meet all of the following criteria:<br><br>1. Patients must give written informed consent according to local guidelines prior to any screening procedures.<br><br>2. Patients must not be eligible for another ongoing INC424 clinical trial.<br><br>3. Male or female patients aged ≥ 18 years of age.<br><br>4. Patients must be diagnosed with PMF, PPV-MF or PET-MF, according to the 2008 World Health Organization criteria International Standard Criteria (Appendix I), irrespective of JAK2 mutation status.<br><br>5. Patients with PMF requiring therapy must be classified as high risk (3 prognostic factors) OR intermediate risk level 2 (2 prognostic factors, no more), OR intermediate risk level 1 (1 prognostic factor, no more) with an enlarged spleen at the screening visit (assessment to occur at the Screening Visit).. The prognostic factors, defined by the International Working Group (Cervantes 2009) are described in Section 1.1 and Section 5.2 and should be evaluated at the Screening Visit.<br><br>6. Patients with Intermediate-1 and splenomegaly, must have a palpable spleen measuring 5 cm or greater from the costal margin to the point of greatest splenic protrusion.<br><br>7. Patients with a peripheral blood blast percentage count of < 10%.<br><br>8. Patients with adequate liver function defined as total bilirubin or direct bilirubin ≤ 2.0 x ULN, and ALT ≤ 2.5 x ULN. |

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| | 9. Patients with adequate renal function defined as serum creatinine ≤ 2 x ULN.<br><br>10. Patients with an ECOG performance status of 0, 1, or 2 (Appendix IV).<br><br>11. Women of childbearing potential must have had a negative serum pregnancy test within 14 days prior to the administration of study drug.<br><br>12. Patients must have recovered or stabilized sufficiently from any adverse drug reactions associated with prior treatments before beginning treatment with INC424.<br><br>13. Fedratinib pretreated patients with documented complete physical examination including full neurologic examination and cardiology assessment, thiamine level testing, and MRI of the brain if indicated based on signs or symptoms. Patients pretreated with fedratinib should have completed or be receiving thiamine supplementation according to the investigator's instructions.<br><br>**Exclusion Criteria**<br>Patients eligible for this study must not meet any of the following criteria:<br><br>1. Patients eligible for hematopoietic stem cell transplantation (suitable candidate and a suitable donor is available).<br><br>2. Patients with a history of malignancy in the past 3 years, except for treated early stage squamous or basal cell carcinoma in situ.<br><br>3. Patients receiving any medications listed in the "Prohibited Medications" listing (Appendix VI).<br><br>4. Impairment of GI function or GI disease that may significantly alter the absorption of INC424 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).<br><br>5. Patients with cardiac disease which in the Investigator's opinion may jeopardize the safety of the patient or the compliance with the protocol.<br><br>6. Patients with currently uncontrolled or unstable angina, rapid or paroxysmal fibrillation or recent (approximately 6 months) myocardial infarction or acute coronary syndrome.<br><br>7. Patients with clinically significant bacterial, fungal, parasitic or viral infection that requires therapy. Patients with acute bacterial infections requiring antibiotic use should delay screening/enrollment until the course of antibiotic therapy has been completed.<br><br>8. Patients with known active hepatitis A, B, C or who are HIV-positive.<br><br>9. Patients with inadequate bone marrow reserve at baseline visit as demonstrated by:<br>(a) ANC that is ≤ 1000/μL.<br>(b)Platelet count that is <50,000/μL without the assistance of growth factors, thrombopoietic factors or platelet transfusions.<br><br>10. Patients with any history of platelet counts < 50,000/μL or ANC <500/μL except during treatment for a MPD or treatment with cytotoxic therapy for any other reason.<br><br>11. Patients with coagulation parameters (PT, PTT, INR) >1.5 x ULN.<br><br>12. Patients with known hypersensitivity to INC424 or other JAK1/JAK2 inhibitors, or to their excipients.<br><br>13. Patients under ongoing treatment with another investigational medication within 30 days of screening or having been treated with fedratinib within 14 days of screening. |

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| | 14. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until termination of gestation, confirmed by a positive βHCG laboratory test (> 5 mIU/mL).<br><br>15.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 28 day safety follow up. Highly effective contraception methods include:<br><br>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<br><br>Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total 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<br><br>Male sterilization (at least 6 months prior to screening). the vasectomized male partner should be the sole partner for that subject.<br><br>Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception<br><br>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), total 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.<br><br>Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they are using highly effective contraception methods (see ) defined as:<br><br>- Total abstinence and<br>- Female sterilization<br>- Combination of any two of the following (a+b or a+c or b+c):<br><br>(a) Use of oral, injected or implanted hormonal methods of contraception<br>(b) Placement of an intrauterine device (IUD) or intrauterine system (IUS)<br>(c) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository<br><br>- The duration of required highly effective contraception is: during dosing and for 5 times the terminal half-life of INC424 (i.e. 29 hours). The mean elimination half-life of INC424 is approximately 3 hours and the mean half-life of INC424 and metabolites is approximately 5.8 hours.<br><br>16. Patients who are unable to comprehend or are unwilling to sign an ICF.<br><br>17. Patients with active alcohol or drug addiction that would interfere with their ability to comply with the study requirements.<br><br>18. Patients with any concurrent condition that, in the Investigator's opinion, would |

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| | jeopardize the safety of the patient or compliance with the protocol.<br><br>19. In the case of ruxolitinib pretreated patients, ruxolitinib primary resistant patients defined as:<br>● No spleen reduction within the first 12 weeks after front line therapy with ruxolitinib AND<br>● No reduction in symptoms within the first 12 weeks after first-line treatment with ruxolitinib.<br>20. In the case of ruxolitinib pretreated patients, patients discontinuing ruxolitinib due to a Grade 4 AE related or suspected to be related to ruxolitinib. |
| **Patient numbering** | Each patient is identified in the study by a Patient Number (Patient No.) that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout their participation in the trial.<br><br>The Patient No. consists of the Center Number (Center No.) [as assigned by Novartis to the investigative site] with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the ICF, the patient is assigned to the next sequential Patient No. available to the investigator through the Oracle Clinical RDC interface.<br><br>Patient who may have been enrolled in CINC424A2401 before being enrolled in fedratinib trial and being screened for CINC424A2401 will be assigned a new patient number as described above.<br><br>Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed, even if the patient is re-screened.<br><br>Patients will begin protocol treatment with INC424 within 7days of meeting eligibility criteria. If a patient does not begin study treatment following enrollment, the reason for withdrawal must be determined and the Sponsor's site monitor will be notified as soon as possible. |
| **Investigational and control drugs** | Investigational drug refers to INC424. There is no control drug in this open-labeled study. |
| **Dose, regimen, treatment** | The starting dose of INC424 tablets will be determined based on a patients Baseline platelet count as follows:<br>- Patients with a Baseline platelet count > 200,000/μL will begin dosing at 20 mg BID (See Section 6.1.1)<br><br>- Patients with a Baseline platelet count of 100,000/μL to 200,000/μL (inclusive) will begin dosing at 15 mg BID See Section 6.1.1)<br><br>- Patients with a Baseline platelet count of 50,000/ μL – <100,000/μL /μL will begin dosing at 5 mg BID. See Section 6.1.1)<br><br>Patients with a platelet count <50,000/μL are ineligible for the study.<br>The oral dose listed above will be administered BID continuously until either:<br><br>- Disease progression;<br>- Transplant;<br>- Unacceptable toxicity;<br>- Death;<br>- Discontinuation from the study for any other reason;<br>- Withdrawal of consent;<br>- Physician decision;<br>- Until 24-months after LPFV; or<br>- Until the drug is commercially available, whichever occurs first.<br>The trial may be stopped in any single country at any time ahead of other countries.<br><br>Dose escalation is permitted for patients receiving starting doses of 15 – 20 mg BID doses of INC424 with inadequate responses following at least 4 weeks of therapy if **all** of the |

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| | following conditions are met:<br><br>- Palpable spleen length below the costal margin that has been reduced by < 40% at the Week 4 visit relative to baseline.<br><br>- Platelet count at the Week 4 blood draw is > 150,000/µL and platelet count has never been < 150,000/µL at a prior laboratory assessment while receiving INC424 (Figure 6-1).<br><br>- ANC levels have remained ≥1000/µL since enrollment in the study.<br><br>Additional dose increases beyond the week 4 dose escalation for patients who start on 15 – 20 mg BID of INC424 are permitted, at the discretion of the investigator, as follows:<br><br>- The patient must not have had a prior safety-related dose reduction.<br><br>- The patient must have had a platelet count ≥ 150,000/µL at every assessment since baseline.<br><br>- The patient must have had ANC ≥ 1000/µL at every assessment since baseline.<br><br>- The dose increase may only be an increase of 5 mg BID.<br><br>- The total dose may never exceed 25 mg BID.<br><br>For those patients who start INC424 treatment at a dose of 5 mg BID, dose increases can be made, at the discretion of the investigator, as described below. The dose can be escalated 5 mg once a day starting at week 4, and thereafter no more than every two weeks ONLY if:<br><br>- The patient must not have had a prior safety-related dose reduction.<br><br>- Platelet count remains ≥ 50,000/µL since last lab scheduled visit.<br><br>- ANC > 1000/µL since last scheduled visit.<br><br>- No dose reduction or interruption for safety occurred in the preceding weeks after the last planned visit.<br><br>- The dose increase may only be an increase of 5 mg o.d. i.e., from 5 mg PO BID to 5 mg QAM and 10 mg QPM.<br><br>- The total dose may never exceed 25 mg BID.<br><br>Following a dose increase, platelet count and ANC levels should be assessed approximately 2 weeks after the dose adjustment. If a regularly scheduled Study Visit does not coincide with this required blood draw, an unscheduled Interim Visit should be held to collect samples for hematology.<br><br>Dose interruption or dose reduction (Section 6.2.2) is mandatory as follows for patients who start on dose of 15 – 20 mg BID:<br><br>Dosing must be held if platelet counts decline to < 50,000/µL (Grade 3 laboratory abnormality by CTCAE v. 3.0, or if ANC falls below 500/µL while receiving INC424.<br><br>Doses should be decreased for platelet count values < 125,000/µL as shown in Table 6-2 with optional restarting or resuming prior dose after recovery Section 6.2.3 In order to provide sufficient data to make dose adjustment decisions, it is recommended that hematology parameters be obtained at least weekly for platelet count <100,000/µL or ANC < 1000/µL and at least two times weekly for platelet count < 50,000/µL or ANC <500/µL.<br><br>Dose interruptions or dose reductions for patients starting INC424 5 mg BID: dose |

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| | interruptions are made according to the platelet count as follows (see Table 6-2 and Table 6-3):<br><br>- If platelets ≤ 25,000/µL and/or ANC < 500/µL): hold treatment<br>- If platelets > 25,000 - < 50,000/µL: reduce the INC424 dose by 5 mg o.d. increments<br><br>The patients should then be reassessed the following month. If the platelet count improves, the patient can restart treatment, and if the platelet count does not improve the patient should be withdrawn from the study |
| **Dose, regimen, treatment, continued** | The dose strategy in Table 6-4 covers the starting doses (15 mg BID and 20 mg BID) and possible doses after an increase for inadequate efficacy (20 mg BID and 25 mg BID).<br><br>Patients are free to withdraw consent and discontinue participation in the study at any time, without prejudice to further treatment. A patient's participation in the study may also be discontinued at any time at the discretion of the Investigator or Sponsor. The following are reasons the Investigator or Sponsor may remove a patient from the study:<br><br>- The patient requests discontinuation.<br><br>- The Investigator thinks a change of therapy would be in the best interest of the patient.<br><br>- The patient experiences an intolerable AE.<br><br>- The patient is found to be not eligible for further study treatment.<br><br>- The patient is non-compliant with study requirements.<br><br>- The patient becomes pregnant during the study or if a patient fails to use adequate birth control (for those patients who are able to conceive).<br><br>- The patient requires a medication prohibited by the protocol. |
| **Supply, preparation, and administration** | INC424 is provided as a 5 mg or 10 mg tablet. The bottles are labeled in the local language. Once commercially available, the drug may be provided locally. The study medication is referred to as INC424 5 mg or 10 mg tablet on the label. INC424 is to be administered orally, without regard to food, in an outpatient setting in accordance with specified dosing schedules. The bottles of tablets should be stored at room temperature, 15°C to 30°C (59°F to 86°F). |
| **Visit schedule and assessments** | Refer to Table 7-1 in protocol. |
| **Efficacy assessment(s)** | Response to treatment and disease progression will be assessed by PE, specifically assessing changes in spleen length by palpation. Disease assessment will be performed at screening/baseline, month 1, 2 month 3, and every 3 months thereafter; and at discontinuation of study drug.<br><br>In patients without splenomegaly, efficacy assessments will only be provided by the patient reported outcomes that measures symptoms of the disease. |
| **Special safety assessment(s)** | AEs of all grades, Grade 3/4 AEs, SAEs; laboratory assessments (hematology, serum chemistry, coagulation), vital signs (blood pressure, heart rate, respiratory rate, temperature); cardiac assessments. |
| **Patient reported outcomes** | The FACT-Lym (version 4) and the FACIT-Fatigue Scale will be used to document patient reported symptoms including physical well-being, social/family well-being, emotional well-being, functional well-being, constitutional symptoms and fatigue. |
| **Medical Resource Utilization** | MRU will be collected up to week 48 to document number of hospitalizations, emergency room visits, outpatient office visits general practitioner, specialist, urgent care visits; transfusions; concomitant medications; and splenectomy/splenic irradiation. |
| **Pharmacokinetics** | N/A |
| **Biomarker assessments** | N/A |

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| **Exploratory Biomarker pharmacodynamic studies involving tumor samples** | N/A |
| **Optional Biomarker studies on additional or remaining samples** | N/A |
| **DMC** | Not applicable |
| **Statistical methods and data analysis** | The primary study objective (to collect safety data) and secondary objective being descriptive; only descriptive statistics will be provided.<br><br>Data from all centers will be combined and analyzed together.<br>The primary analysis will be performed after all patients have either completed 24 months of treatment or have been prematurely discontinued from the study.<br><br>**Analysis sets:**<br>Full Analysis Set (FAS) consists of all patients who received at least one administration of study drug.<br><br>Safety set consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.<br><br>Per protocol set: consists of all FAS patients without any major protocol deviation. Rules for identifying major protocol deviations would be detailed in Report Analysis Plan.<br><br>**Analysis methods**<br>**Primary objective**<br>The analysis will provide the incidence of treatment-emergent AEs (occur during treatment, including the 28 safety follow-up days) or AEs that worsen on treatment. Death rate (any death) at end of study will be summarized.<br><br>**Secondary objectives: Efficacy**<br>The proportion of patients by best overall response category will be summarized. Proportion of responders will be estimated and its 95% confidence intervals provided.<br><br>- Change in spleen length from Baseline to end of each visit/month of therapy and at end of treatment will be described using descriptive statistics and by relevant change categories.<br><br>- Change in WBC and platelet count changes from Baseline to end of each visit and at end of treatment.<br><br>- Shift in fibrosis in the bone marrow from Baseline to worst/best value on study will be described.<br><br>- PFS, LFS, and OS will be estimated with the Kaplan Meier method and 95% confidence intervals will be provided for the estimated median.<br><br>**Secondary objectives: MRU**<br>Frequency of hospitalization, of emergency room visits, general practitioner, specialist, or urgent care visits,, and of splenectomy and splenic irradiation will be summarized at end of each treatment quarter.<br><br>Overall duration of hospitalization at end of study will be summarized<br><br>The proportion of patients who are transfusion dependent as well as the proportion of patients whose transfusion status (dependent or independent) changed (from dependent |

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| | to independent or vice versa) will be tabulated with summary statistics.<br><br>**Quality of Life Assessments**<br>ECOG score will be summarized descriptively by visit. A shift summary including number and % of patients will be produced by visit for baseline vs. post-baseline scores.<br><br>Data from FACT-Lymphoma (version 4) Scores will be analyzed in the sum scores. Change and % change from baseline to each scheduled visit will be calculated. The treatment effect on FACT-Lymphoma Scores over time will be estimated using repeated measurements analysis.<br><br>Data from FACIT Scores will be analyzed in the sum scores. Change and % of change from baseline to each scheduled visit.<br><br>Time to first improvement will be estimated for ECOG performance score and for selected scales for FACT-Lymphoma (version 4) and FACIT scale according to minimally important difference (MID).<br><br>[redacted] |
| **Interim analysis (IA)** | An interim analysis will be performed to closely monitor safety, and ensure an appropriate risk/benefit ratio in the patient population with low platelet counts, between 50,000 and <100,000/μL /μL. In order to adequately assess the risk/benefit ratio, this analysis will also be performed on a non-low platelet population (patients with baseline platelet count ≥100,000/μL), which will be further detailed in analysis plan, who will serve as an internal reference population. This interim analysis will take place when 50 patients with low platelets have completed 6 months of treatment<br><br>Analyses will also be performed if needed to fulfill regulatory obligation, to comply with post-approval commitments or for publication purpose. |

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# 1 Background

INC424 phosphate is an inhibitor of the Janus kinase family of protein tyrosine kinases (JAKs) that is currently under development for treatment of primary myelofibrosis (PMF), post polycythemia vera myelofibrosis (PPV MF) and post essential thrombocythemia myelofibrosis (PET-MF). INC424 (ruxolitinib, Jakafi®) was approved by the FDA on 16 November 2011, and approved by the EMA on 31 August 2012, for the treatment of intermediate or high-risk myelofibrosis, including primary myelofibrosis, post–polycythemia vera myelofibrosis and post–essential thrombocythemia myelofibrosis.

## 1.1 Overview of myelofibrosis and myeloproliferative neoplasms and current treatment options

Myelofibrosis (MF) is a clonal hematologic neoplastic disease characterized by the presence of megakaryocyte proliferation and atypia, usually accompanied by either reticulin and/or collagen fibrosis (Tefferi A (2008)), splenomegaly, anemia, and debilitating constitutional symptoms that include fatigue, weight loss, pruritus, night sweats, fever, and bone, muscle, or abdominal pain (Mesa RA, Niblack J, Wadleigh M, et al (2007), Abdel-Wahab OI, Levine RL (2009)). MF can either be primary in origin (primary myelofibrosis, or PMF) or result from progression of polycythemia vera or essential thrombocythemia vera (Tefferi A (2008)). The median age at diagnosis of MF is approximately 65 years. Patients with myelofibrosis have shortened survival that ranges from a median of approximately 2 years to 11 years depending on the presence of certain risk factors that define their risk category including age, anemia, leukocytosis, etc.

Several prognostic risk scores that are based on survival outcomes have been developed in MF to better define treatment choices for physicians and therefore improve patient management. The International Prognostic Scoring System (IPSS) was developed by the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) (Cervantes F, Dupriez B, Pereira A, et al (2009)). The IPSS is used at diagnosis and employs five hematologic and clinical variables (age, leukocytosis, anemia, peripheral blood blasts and constitutional symptoms) to stratify patients in a low, intermediate-1, intermediate-2 and high-risk category. The dynamic IPSS (DIPSS) was subsequently developed to be used for patients evaluated after MF diagnosis (Gangat et al 2011). The DIPSS relies upon the same five variables as IPSS but utilizes the predictive value of selected cytogenetic abnormalities. These scoring systems are expected to facilitate categorizing patients to different risk groups, and thus assist physicians in recommending optimal treatment management plans.

All currently available pharmacologic treatments are either directed towards the management of MF-originated anemia or the treatment of MF-symptoms including splenomegaly. As these treatments do not cure or modify the disease progression of MF, they are mostly used to treat patients in the higher risk categories. MF patients in the lower risk categories (IPSS Low and Int-1), by virtue of a relatively asymptomatic disease and an indolent disease course, are managed through active surveillance or a ‘watch and wait’ approach until appearance of bothersome symptoms or the definitive progression to the higher risk groups. Allogeneic stem

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cell transplantation is the only curative option, but it is often associated with a high rate of mortality and morbidity (Kroger 2008). Other available treatments include splenectomy, involved field radiotherapy, erythropoiesis stimulating agents, androgen preparations, thalidomide and its analogs, hydroxyurea. More recent advancements in MF treatment include the discovery of ruxolitinib, a Janus Kinase (JAK)1 and JAK2 inhibitor. Ruxolitinib is one of the first treatments in MF that has demonstrated rapid and durable reductions in MF- related splenomegaly, improvement in disease-related symptoms and offers a distinct survival benefit (Vannucchi et al 2015).

The recent years have witnessed major advances in the molecular understanding of MF, first with the identification of JAK2 and MPL mutations (Kilpivaara, Levine 2008) and more recently the calreticulin (CALR) gene (Klampfl T et al 2013), all of which are associated with an activation of the Janus Kinase-Signal Transducer & Activator of Transcription (JAK-STAT) pathway. In addition, as also shown in other myeloid malignancies, mutations in a multiplicity of other genes involved in the epigenetic and spliceosome regulatory machineries have been reported in MF across IPSS risk categories and shown to have a negative prognostic impact.

A recent study evaluated 879 PMF patients to determine the individual and combinatorial prognostic relevance of somatic mutations. Analysis was performed in 483 European patients and the seminal observations were validated in 396 Mayo Clinic patients. Samples from the European cohort, collected at the time of diagnosis, were analyzed for mutations in ASXL1, SRSF2, EZH2, TET2, DNMT3A, CBL, IDH1, IDH2, MPL and JAK2 (Vannucchi et al 2013a). A specific sub-group of mutations were identified (ASXL1, EZH2, SRSF2 and IDH*)* that may be predictive of PMF patients who are at risk for premature death or leukemic transformation. These mutations are classified as the 'high molecular risk' category (HMR) in PMF based on the presence of at least one of the five prognostically detrimental mutated genes.

[Guglielmelli et al.] further evaluated the additional prognostic value of the number of mutated genes. A total of 797 patients were recruited from Europe (n=537) and the Mayo Clinic (n=260). In the European cohort, 167 (31%) patients were categorized as HMR: 127 (23.6%) had one and 40 (7.4%) had two or more mutated genes. The presence of two or more mutations predicted the worst survival: median 2.6 years (hazard ratio (HR) 3.8, 95% confidence interval (CI) 2.6‑ 5.7) vs 7.0 years (HR 1.9, 95% CI 1.4‑ 2.6) for one mutation vs 12.3 years for no mutations (Figure 1-1, Guglielmelli et al 2014a). The presence of two or more mutations was also associated with shortened leukemia-free survival (HR 6.2, 95% CI 3.5‑ 10.7). Overall, the recent studies demonstrate that patients with PMF harboring mutations in any one of the five prognostically detrimental genes (ASXL1, EZH2, SRSF2 and IDH1/2) constitute an IPSS/DIPSS-plus independent HMR category with shorter survival and greater risk of acute myeloid leukemia (AML) progression compared with the low molecular risk (LMR) patients. These findings therefore identify a clinically relevant subgroup of MF patients with HMR mutations, who despite being minimally symptomatic (including less severe splenomegaly) and thus categorized to harbor a lower risk disease through the IPSS or DIPSS scoring systems, may require earlier intervention with treatments that would prevent or delay their disease progression and leukemic transformation and potentially improve their survival. The majority of HMR positive patients with minimally symptomatic disease (Early

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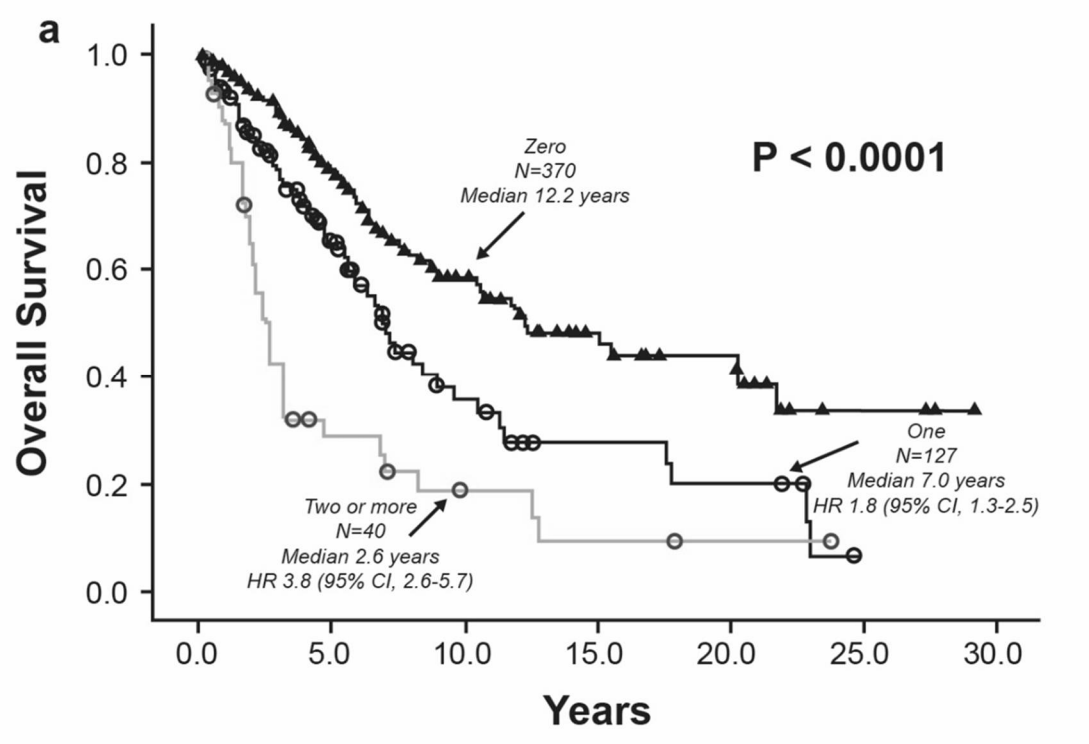
MF) are currently not treated until symptoms present more aggressively. These HMR positive early MF (HMR+ EMF) patients are in need of therapy that can delay progression and therefore have an unmet medical need.

Currently, ruxolitinib is the only treatment that has shown evidence through prospective randomized trials to not only reduce symptom burden and splenomegaly but also confer a longer term survival advantage and delay time to leukemia transformation (Vannucchi et al 2015). A retrospective analysis conducted by Guglielmelli et al in the COMFORT II study, showed that HMR status did not affect the likelihood of obtaining a treatment benefit with ruxolitinib, suggesting that the clinical efficacy and survival improvement observed with ruxolitinib in MF patients may occur independently of the underlying molecular pattern. These observations were however confined to patients in the higher risk categories (IPSS Int-2 and High) and therefore currently not established in the lower risk categories. This study will investigate the effect of JAK inhibition with ruxolitinib in a patient population with earlier MF disease harboring HMR mutations. It is to be noted that the selection of patients with HMR mutations is solely intended to identify a subset of patients with an intrinsically aggressive MF disease, with poor prognosis and hence an unmet medical need for appropriate therapeutic intervention. The HMR test in the study is not intended for preselecting patients who are more likely to respond to ruxolitinib or tolerate the treatment.

**Figure 1-1 Prognostically detrimental 'HMR' mutations and survival in PMF: Kaplan Meier Plots**

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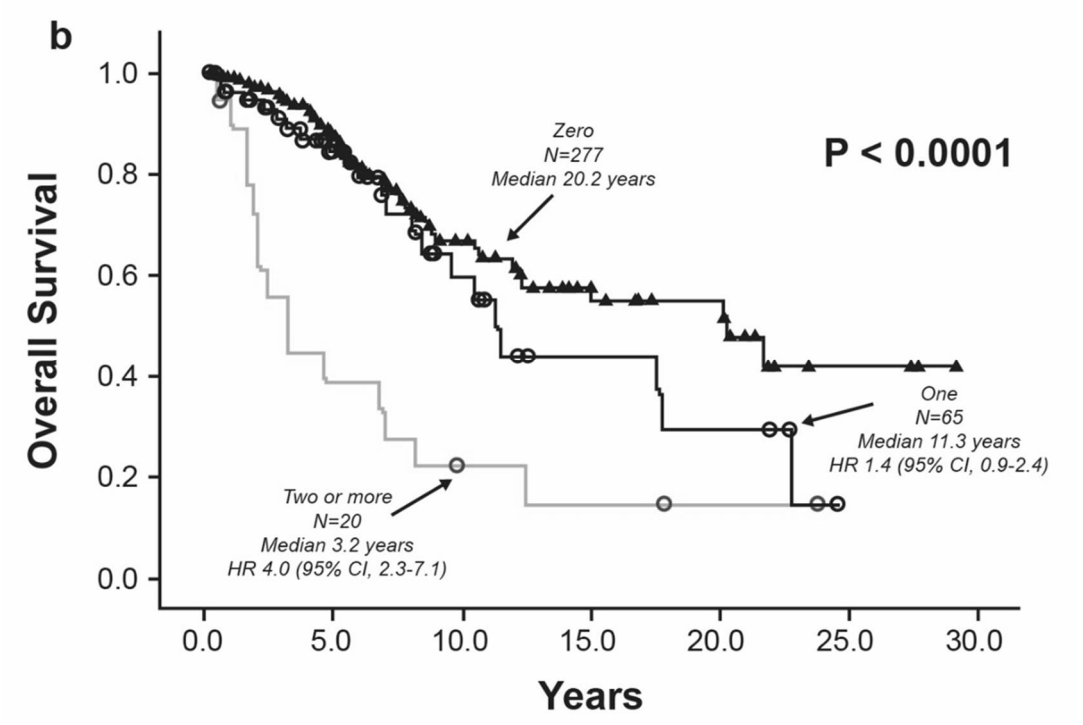


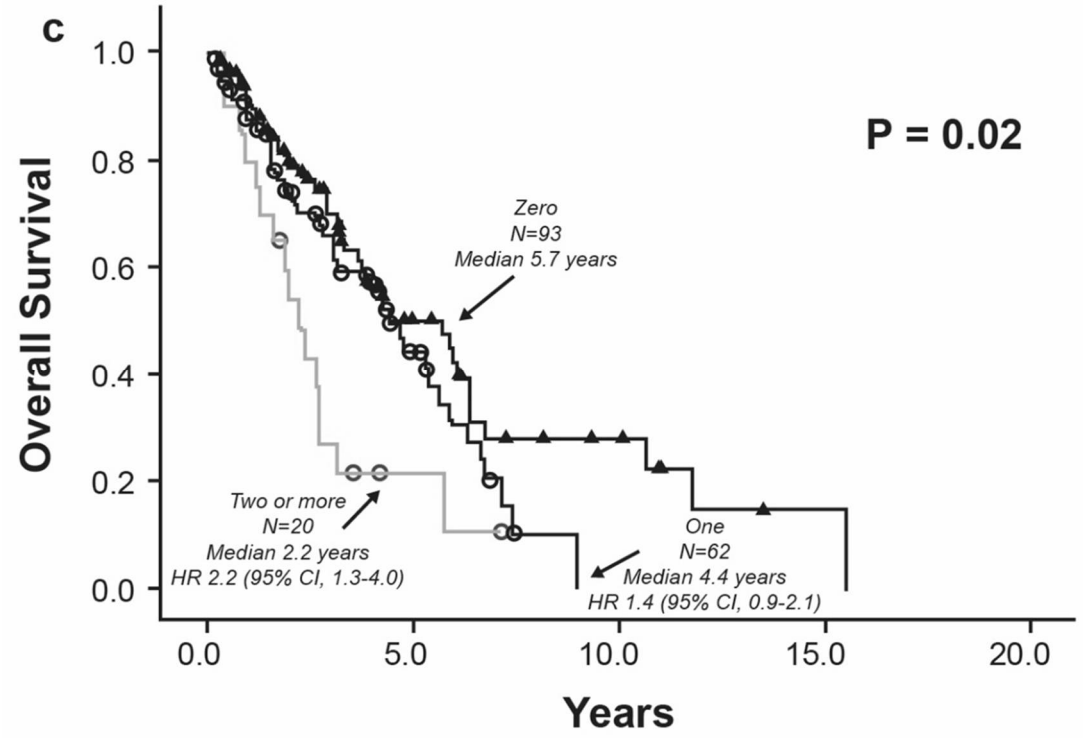


a – Overall survival stratified by zero, one and two/more prognostically detrimental mutations (HMR).

b – Overall survival for IPSS low risk categories (Low and intermediate-1) stratified by number of HMR mutations.

c - Overall survival for IPSS high risk categories (intermediate-2 and high) stratified by number of HMR mutations.

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## 1.2 Inhibition of Janus Kinases (JAK) in MPN

A key feature of MPNs is the dysregulation of JAK/STAT signaling. The JAK/STAT pathway is involved in normal hematopoiesis, inflammation, and immune function (Ghoreschi 2009). The 4 members of the JAK family - JAK1, JAK2, JAK3, and TYK2 - are non-receptor tyrosine kinases that play a central role in signal transduction initiated by cytokines (e.g., interleukin and interferon signaling), growth factors, and hormones (Ghoreschi 2009). Specifically:

- JAK1 - role in lymphopoiesis and cytokine response; ubiquitously expressed
- JAK2 - role in erythropoiesis; ubiquitously expressed
- JAK3 - role in lymphocyte development and proliferation and immune response; expressed primarily in hematopoietic cells
- TYK2 - role in mediation of cytokine signals; ubiquitously expressed

Upon ligand binding, the receptor undergoes conformational changes that allow JAK activation and result in receptor homodimerization (i.e., JAK2/JAK2) or heterodimerization (ie, JAK1/JAK2) (Vainchenker 2008). The activated JAKs create docking sites on the receptor for STAT (signal transducers and activators of transcription) proteins. STAT proteins, once activated, dissociate from the receptor, dimerize, and translocate into the nucleus to initiate transcription of target genes (Ghoreschi 2009). Given the importance of this interaction, this pathway is also known as the JAK/STAT pathway.

Dysregulation of the JAK pathway can occur in a number of ways. Ligand-independent activation of the pathway can occur due to mutations in the JAK receptor. In addition, mutations in or activation of other modulators of the signaling pathway can result in pathway overactivation. Regardless of a particular mutation's presence or absence, dysregulation of the JAK pathway is a hallmark of MPNs. The majority of patients with MF, PV, and ET bear a somatic activating mutation in *JAK2* whereby a G>T nucleotide exchange in exon 14 at position 1849 results in a substitution of valine by phenylalanine at amino acid 617 (JAK2 V617F) (Tefferi 2009a).

Recent genome-wide association studies suggest that individuals can have a genetic predisposition to the development of JAK2 V617F-positive MPNs. Specific haplotypes have been identified that preferentially acquire the JAK2 V617F mutation and confer susceptibility to MPNs, which may partially explain the phenotypic diversity observed in carriers of the mutation (Tefferi 2009a, Olcaydu 2009).

With frequencies of greater than 95% in PV and approximately 50% in MF and ET (Tefferi 2009a), the presence of this mutation is a major criterion in the diagnosis of these diseases. Although the JAK2 V617F-activating mutation is the most commonly observed mutation in MPNs, it is not the only JAK pathway-activating mutation noted in MPN patients. Mutations in exon 12 have also been noted, mostly in PV patients (Scott 2007). Indeed, virtually all JAK2 V617F-negative PV patients bear JAK2 exon 12 mutations (Schnittger 2009). Of note, these mutations affect the pseudokinase domain or a proximal region ("exon 12" mutations) but not the kinase domain.

Abnormal activation of JAK1 has also been noted in MF patients (Quintas-Cardama 2010). In addition to alterations in JAK1 and JAK2, alterations in other members of the JAK pathway

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have been detected in MPN patients. These alterations include a somatic activating mutation in the JAK2-associated thrombopoietin receptor gene MPL at codon 515 (*MPL W515L/K*) and various mutations in LNK, a negative regulator of JAK/STAT signaling (Oh 2010, Patnaik 2010). Clearly, JAK pathway dysregulation, regardless of mutational status, is a key pathophysiological feature of MPNs. As the most prevalent mutation in MPNs, the prognostic impact of the JAK2 V617F mutation has been well-characterized. In both PV and ET, the presence of JAK2 V617F is associated with a higher risk of thrombosis and thrombotic effects, and its presence indicates a higher risk of transformation to post-PV/ET MF (Barosi 2007, Tefferi 2007c, Vannucchi 2007, Basquiera 2009). PMF patients with the JAK2 V617F mutation have higher leukocyte counts and a history of thrombosis (Barosi 2007).The V617F mutation also predicts large splenomegaly, need for splenectomy, and an increased risk of leukemic transformation in PMF patients (Barosi 2007). The clinical course of PV patients with JAK2 exon 12 mutations appears to be similar to that of patients with the JAK2 V617F mutation (Tefferi 2010b).

## 1.3 Overview of INC424

INC424 represents a novel, potent, and selective inhibitor of JAK1 and JAK2.

INC424 potently inhibits JAK1 and JAK2 [half maximal inhibitory concentration (IC) 0.4 to 1.7 nM], yet it does not significantly inhibit (< 30% inhibition) a broad panel of 26 kinases when tested at 200 nM (approximately 100 x the average $IC_{50}$ value for JAK enzyme inhibition) and does not inhibit JAK3 at clinically relevant concentrations. Pharmacological data obtained in *in vivo* model systems support the potential utility of orally administered INC424 in the treatment of malignancies, including MPDs such as PMF, PPV-MF, and PET-MF. INC424 retains activity against the JAK2V617F mutant and is effective in reducing splenomegaly in mice inoculated with cells carrying this mutation. Additional details as to the *in vivo* pharmacology of INC424 may be found in the [Investigator's Brochure] (IB).

Dysregulated JAK-STAT signaling, via upregulation of JAK1 and JAK2 or gain of function mutations such as JAK2V617F, has been implicated as drivers of BCR-ABL-negative myeloproliferative neoplasms (MPN), namely myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET). Ruxolitinib, which is jointly developed in hematology and oncology indications by Novartis Pharma AG (Switzerland) and Incyte Corporation (USA), specifically binds to and inhibits JAK1, JAK2 and mutated JAK2V617F, leading to inhibition of growth factor-mediated cell signaling and tumor cell proliferation. Given this mechanism of action of ruxolitinib as a JAK inhibitor and the role played by dysregulation of the JAK pathway in the pathogenesis of MPNs, the primary clinical development plan for ruxolitinib focused on studies to support regulatory approval in these disorders.

Ruxolitinib is currently approved under the trade name of 'Jakavi' in over 90 countries 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). The use of ruxolitinib to treat polycythemia vera (PV) patients who are resistant to or intolerant of hydroxyurea is currently under regulatory review worldwide based on the results from the RESPONSE study. So far approval in this second indication was granted in more than 45 countries including EU and Switzerland. Ruxolitinib is also approved in the USA under the trade name of 'Jakafi' and is indicated for

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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.

### 1.3.1 INC424 pharmacokinetics

Fifteen Phase I , nine Phase II and three Phase III clinical studies (two in MF, one in PV) provided clinical pharmacology data on ruxolitinib in healthy volunteers and in patients with MF, ET, PV, subjects with renal or hepatic impairment, prostate cancer, pancreatic cancer, multiple myeloma (MM) or rheumatoid arthritis (RA).

Oral absorption of ruxolitinib is rapid and nearly complete, with ≥95% absorption indicating high *in vivo* permeability in the human gastrointestinal tract, consistent with a Biopharmaceutical Classification System (BCS) Class I compound. Mean peak plasma concentration (Cmax) is achieved 1-2 h post-dose. The effect of food on ruxolitinib exposure is minimal and is not expected to be clinically significant; as a result, the drug may be administered either with or without food.

Dose proportional exposure is observed between 5 and 200 mg dose range with linear pharmacokinetics (PK). Plasma protein binding is approximately 97% *in vitro*. There is moderate distribution to organs and tissues with no long-term retention of drug-related material in preclinical species and limited drug penetration into the central nervous system (CNS) or across the blood-brain barrier. There was >95% [$^{14}$C] drug recovery in a mass balance study with 74% and 22% of the dose excreted in urine and feces of healthy subjects, respectively. Less than 1% of the administered dose is recovered in urine and feces as unchanged parent drug. The mean terminal elimination half-life (T1/2) is ~3 h with no appreciable accumulation of either parent or metabolites with twice daily dosing.

Metabolism is predominantly via the cytochrome P450 isozyme CYP3A4 to yield oxygenated and subsequent conjugated metabolites. Oxidative metabolites of ruxolitinib retain pharmacological activity albeit with one half to one fifth of the activity of the parent compound. *Ex vivo* pharmacokinetic/pharmacodynamic (PK/PD) analysis indicates that the total of 8 active metabolites contribute to 18% of the overall PD activity of ruxolitinib.

When administering ruxolitinib with strong CYP3A4 inhibitors, the total daily dose should be reduced by approximately 50%.

No dose adjustment is necessary when co-administering ruxolitinib with strong CYP3A4 inducers. No dose adjustment is necessary when co-administering ruxolitinib with CYP3A4 substrates. Ruxolitinib did not decrease the exposure of a fixed dose oral contraceptive metabolized via the CYP3A4 pathway, thus demonstrating lack of CYP3A4 induction potential.

In patients with severe (creatinine clearance (Clcr) <30 mL/min) and moderate renal impairment (Clcr = 30-59 mL/min), the recommended starting dose based on platelet count should be reduced by approximately 50% to be administered twice a day. Patients on hemodialysis should initiate ruxolitinib with a single dose of 15 mg or 20 mg based on platelet counts on day of hemodialysis with subsequent doses only on hemodialysis days and following each hemodialysis session. Ruxolitinib doses should be titrated based on individual safety and efficacy.

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In patients with mild, moderate or severe hepatic impairment, the recommended starting dose based on platelet count should be reduced by approximately 50% with subsequent dose titration based on individual safety and efficacy.

Ruxolitinib PK in healthy volunteers was largely comparable between Japanese, Chinese and Western subjects and did not lead to a conclusion of meaningful ethnic differences.

Baseline elevations in inflammatory markers such as tumor necrosis factor alpha (TNFα), interleukin (IL)-6, and C-reactive protein (CRP) noted in patients with MF were associated with constitutional symptoms such as fatigue, pruritus, and night sweats. Decreases were observed in these markers over the 24 weeks of treatment with ruxolitinib, with no evidence that patients became refractory to the effects of ruxolitinib treatment

### 1.3.2 INC424 preclinical safety

The toxicologic and toxicokinetic profiles of INC424 were characterized in single and repeat oral dose studies of up to 6 months in duration in rats and dogs. Genetic toxicology, safety pharmacology, and embryo-fetal toxicology studies have also been conducted. In a 6 -month study in rats, doses up to 60 mg/kg/day were evaluated. An adverse decrease in body weight gain was noted in male, but not in female rats. A dose related decrease in lymphocytes was noted. Minimal-to-mild lymphoid depletion in spleens and in mandibular lymph nodes was noted at the 60 mg/kg/day dose level; at lower doses, lymphoid tissues were within normal histologic limits. The no-observed-adverse-effect level (NOAEL) for oral administration of INC424 for 26 weeks was 30 mg/kg/day for the males (unbound AUC 0.119 μM*h), due to adverse effects on body weight at 60 mg/kg/day, and 60 mg/kg/day for female rats (unbound AUC 4.64 μM*h). (Lower parent drug levels in male rats are due to male rat specific isoenzymes 2C11, 2C13 and CYP3A2 which metabolize INC424 to active metabolites). Additional details on rat toxicology studies are available in the [Investigator Brochure].

In the 6-month dog study, doses studied included 0.5, 2.5, 5, and 10 mg/kg/day. Demodectic mange, lymphopenia, eosinopenia, decreases in erythron parameters, moderate to severe cellular depletion of lymphoid tissues, bacterial pneumonia, viral induced papillomas, microscopic invasive demodectic mange, and prostate hypoplasia/atrophy were seen in dogs receiving high dose. Deaths attributed to bacterial pneumonia occurred in 3 of 14 dogs given 10 mg/kg/day. Demodectic mange was observed in several animals given 5 mg/kg/day and, microscopically, in one animal given 2.5 mg/kg/day. These events most likely reflect a response to the immunosuppressive effects of INC424. All tissues were normal in the 0.5 mg/kg/day group. The NOAEL dose was defined at 2.5 mg/kg/day (unbound AUC 0.76 μ M*h) due to minimal findings which were not present in recovery animals. The low dose, 0.5 mg/kg/day, was defined as the no-observed effect-level (NOEL). Additional details regarding dog toxicology studies are available in the [Investigator Brochure].

INC424 was not genotoxic in the bacterial mutagenicity assay, the *in-vitro* chromosome aberration assay, or the *in-vivo* micronucleus assay in rats.

In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated. INC424 was not teratogenic in either the rat or the rabbit. The NOAEL dose for the rat and rabbit study was 30 mg/kg/day. Additional toxicology and safety pharmacology information is available in the [Investigator Brochure].

[redacted]

### 1.3.3 INC424 clinical safety in healthy volunteers

The safety profile for ruxolitinib in the Phase I development program was assessed in over 370 subjects for single or repeat doses. Ruxolitinib has been administered to 40 subjects with various degrees of renal impairment and 32 subjects with various degrees of hepatic impairment. Additionally, a DDI study with methotrexate was completed in 18 RA patients. AEs were, in general, mild and resolved without interventions. In the first-in-human study one subject had hyponatremia after receiving 5 mg ruxolitinib. The hyponatremia was assessed as severe in intensity, unrelated to study medication, reversed within 5 days, and was reported as serious adverse event (SAE).

In the repeat-dose study in healthy subjects, the dose-limiting AE was neutropenia, which occurred at a dose of 50 mg b.i.d. Neutropenia as an AE was noted in three subjects, all receiving the highest dose of ruxolitinib, 50 mg b.i.d. Neutropenia at the Grade 4 level, assessed as severe, led to study drug discontinuation on Day 5 in one subject, and was reported as an SAE. Neutrophil count returned to a normal level 12 days after the final dose of study medication. In two other subjects, neutropenia was Grade 1 or 2, and resolved with dose interruption or during continued dosing. The AE profile was similar for single- and multiple-dose studies, and no differences were observed between males and females. The most frequent (≥2 subjects) treatment-emergent AEs (TEAEs) occurring in the Phase I multiple-dose study were: neutropenia (4.2%), dizziness (2.8%), headache (2.8%) and nausea (2.8%). Overall, in healthy volunteer studies where frequent sampling of the neutrophil count was performed, a transient, reversible decrease in neutrophil count was frequently seen following dosing, which reversed after 12-24 h off drug.

The AE profile of ruxolitinib has also been assessed in 198 healthy volunteers, subjects with various degrees of renal (n=32) or hepatic (n=24) impairment, and in patients with RA (n=59) receiving ruxolitinib: AEs were, in general, mild and resolved without interventions.

A thorough QT study was conducted in 50 healthy subjects. There was no indication of a QT/QTc prolonging effect of ruxolitinib in single doses up to a supra-therapeutic dose of 200 mg indicating that ruxolitinib has no effect on cardiac repolarization.

Please refer to the [Investigator Brochure] for further information.

### 1.3.4 INC424 clinical safety and efficacy in phase I/II trials

#### 1.3.4.1 Phase I/II study of INC 424 in patients with primary, post-PV, or post-ET MF

Study INCB 18424-251 is a completed Phase I/ II open-label study of orally administered INC424 in patients with PMF, PPV MF and PET MF. A total of 153 patients were enrolled at the following oral dosing levels/regimens: starting dose of 25 mg BID followed by escalation up to 50 mg BID; once daily (QD) dosing ranging from 25 mg QD to 200 mg QD. The maximum tolerated doses were identified as 25 mg BID or 100 mg QD, based on dose-limiting thrombocytopenia. In the Phase II component of the trial additional dosing schedules were also evaluated including 25 mg BID (with a reduction to 10 mg BID after 2 cycles [months] of therapy); 10 mg BID, with dose escalation permitted after 3 cycles (months) of therapy; 10 mg BID (in patients with a baseline platelet count of 100 - 200 x $10^9$/L); and 15

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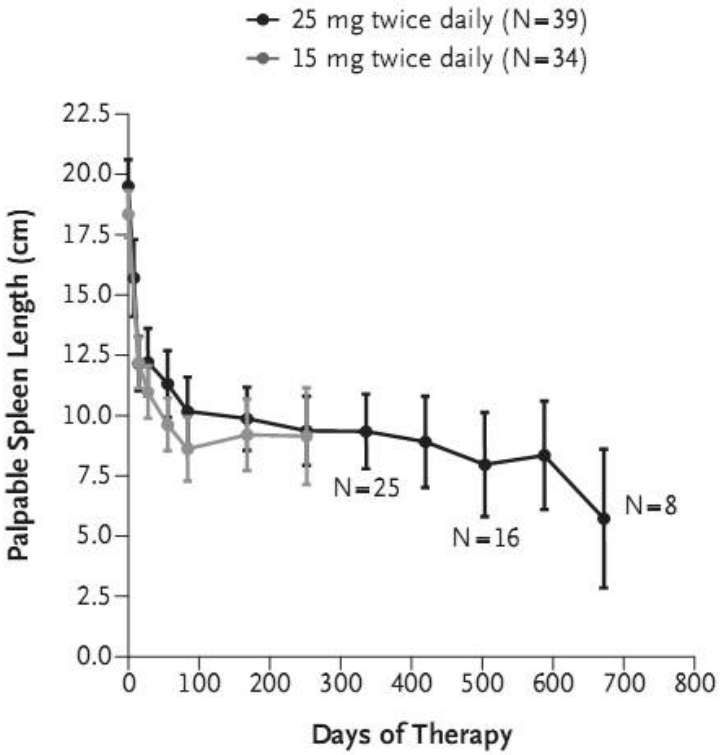
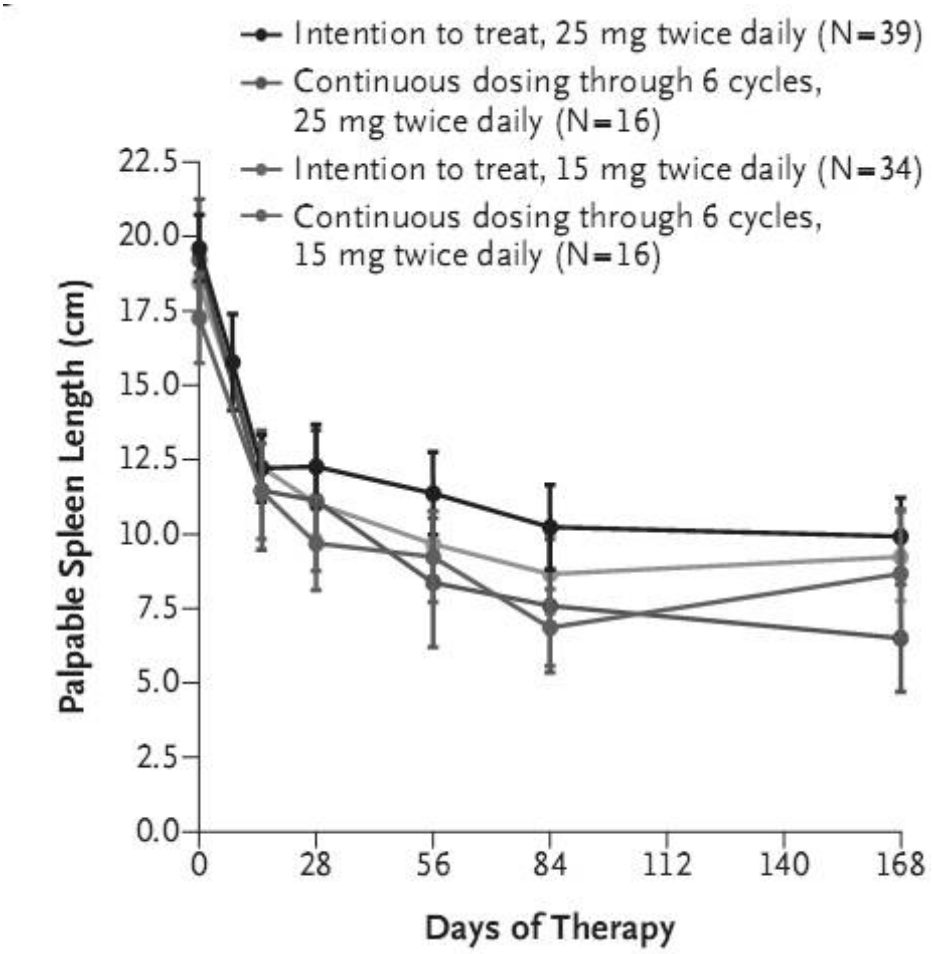
mg BID (in patients with a baseline platelet count of > 200 x $10^9$/L) with dose increases to 25 mg BID (in 5 mg increments). Data from the completed Study INCB 18424-251 demonstrate marked and durable reductions in spleen size. In this study spleen size was measured as palpable length below the left costal margin. Figure 1-2a illustrates the mean reduction in absolute spleen size (measured by palpation) for patients receiving 15 mg BID and 25 mg BID, and Figure 1-2b mean reduction in absolute spleen size (measured by palpation) for patients receiving their originally assigned dose for at least 6 months (Verstovsek 2010b).

**Figure 1-2a Reduction in palpable spleen length in patients receiving different doses of INC424 (Verstovsek 2010b)**




[redacted]

**Figure 1-2b Reduction in palpable spleen length according to INC424 dose when maintained for at least 6 months (Verstovsek 2010b)**

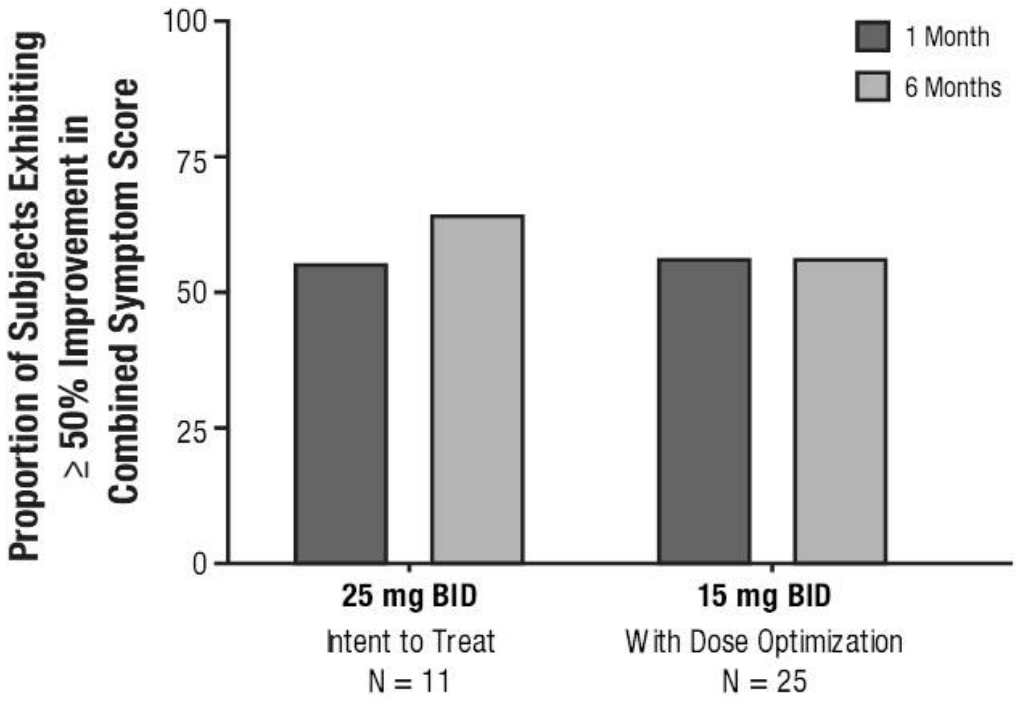



As noted in Figure 1-2a, BID regimens are associated with a prompt decrease in spleen size. Response rates have been demonstrated to be greatest in the BID dosing cohort, with reduced responses in the 50 mg PO QD dosing cohort, and lowest in the 10 mg PO BID dosing cohort (Verstovsek 2010b). The majority of patients had a ≥ 25% reduction in spleen size on therapy (70% in 10 mg BID cohort; 82% in 15 mg BID dosing cohort; 77% in the 25 mg BID cohort). Responses occurred quickly, within 1-2 months of therapy and appear durable (> 1 year in 16 patients for whom data were available at 1.5 years and all 8 patients for whom data were available at 2 years). Best responses were greatest in the 25 mg BID dosing cohort (among patients starting at 25 mg BID and maintaining that dosing schedule), although dose interruptions were common (60%) primarily due to thrombocytopenia. Based on this profile an initial dose of 15 mg INC424 BID is recommended. Spleen reduction occurred regardless of presence/absence of the *JAK2*V617F mutation (data not shown). Progressive MPN are associated with weight loss and cachexia. Dysregulation and abnormal elevation of a variety of pro-inflammatory cytokines may produce a hypercatabolic state which contributes to the weight loss and wasting seen in patients with MF. After an initial weight loss (presumably due to the rapid decrease in splenomegaly and hepatomegaly and loss of ascites and/or pleural effusions) there is a gain in total body weight that appears to be dose-dependent. Weight gains

are present in most patients, including those with body mass index at baseline in the lowest quartile (body mass index below ~ 22).

Improvements in QoL were rapidly demonstrated, typically within 1 month of therapy. The Modified Myelofibrosis Symptom Assessment Form (MFSAF) developed by Mesa et al, and based on an international internet-based survey of over 1000 patients with MPD, was used to probe a range of constitutional symptoms related to splenomegaly (including impaired ability to move around and early satiety) and elevated cytokines (including fatigue, night sweats and pruritus) (Mesa 2007; Appendix VIII). Most patients in the 10 to 25 mg BID dose groups demonstrated a ≥ 50% improvement in total or individual symptom scores per the MF-SAF, which assesses constitutional symptoms including fatigue, night sweats, and pruritus (Figure 1-3). These responses were durable through 6 months of therapy. Symptomatic improvements were similar among the 10, 15, and 25 mg BID dose groups, with improvements in abdominal discomfort and pain accompanying the reduction in spleen size. Additionally, patients started to gain weight as early as after 2 cycles of therapy, with patients in the lowest quartile for body mass index at baseline gaining more weight than those in the highest quartile. Functional improvements in the ability to walk were observed; patients improved their walking ability by 34, 57, and 71 m after 1, 3, and 6 months, respectively (Verstovsek 2010b).

**Figure 1-3 Improvements in combined MFSAF score on INC424**




In summary, INC424 is associated with prompt and marked reduction in spleen size, gains in total body weight, improvement in ECOG status PS and improvement in constitutional symptoms that can be debilitating in this patient population. Refer to the IB and Verstovsek (2010b) for more complete information. INC424 has been well tolerated by this aged population with advanced disease. Nonhematologic adverse events were uncommon and

[redacted]

included diarrhea (5.9%), fatigue (4.3%), headache (3.3%), peripheral edema (2.6%), pain in extremities (2.6%), urinary tract infections (2.6%), dizziness (2.6%), dyspnea (2.6%), asthenia (2%), fever (2%), cardiac murmur (2%), musculoskeletal pain (2%), peripheral neuropathy (2%), edema (2%), anxiety (2%), insomnia (2%), epistaxis (2%), flatulence (2%), and nausea (2%). The majority of these were Grade 1/ 2 CTCAE toxicity. Grade 3/ 4 nonhematologic toxicity included fatigue (1.3%), asthenia (2%), fever (0.7%), anxiety (1.3%) and insomnia (1.3%). Hematologic toxicity consisted primarily of anemia and thrombocytopenia. Thrombocytopenia appeared to be dose related occurring less frequently in the 15 mg BID group (3% Grade 3) than the 25 mg BID group (23% Grade 3; 6% Grade 4). Thrombocytopenia was not related to JAK V617F mutational status. Grade 3 thrombocytopenia occurred in 10% of patients receiving 10 mg BID of INC424, 3% of patients receiving 15 mg BID of INC424, 23% of patients receiving 25 mg BID of INC424, 60% of patients receiving 50 mg BID of INC424, 0% of patients receiving 25 mg QD of INC424, 27% of patients receiving 50 mg QD of INC424; 33% of patients receiving 100 mg QD; and 0% of patients receiving 200 mg QD of INC424. Thrombocytopenia of Grade 4 severity occurred in 0% of patients receiving 10 mg BID of INC424, 0% of patients receiving 15 mg BID of INC424, 6% of patients receiving 25 mg BID of INC424, 20% of patients receiving 50 mg BID of INC424, 0% of patients receiving 25 mg QD of INC424, 9% of patients receiving 50 mg QD of INC424, 0% of patients receiving 100 mg QD of INC424, and 33% of patients receiving 200 mg QD of INC424. Thrombocytopenia occurred more frequently in patients with lower baseline platelet counts ($< 200 \times 10^9$/L), and was reversible within 1 to 3 weeks after dose interruption and/or reduction. New onset anemia occurring in patients who were not transfusion dependent at baseline occurred in 23% of patients across all dosing intervals, and was most common in the 25 mg BID dosing cohort (27%) and least common in the 15 mg BID dosing cohort (8%). Anemia, though dose dependent, largely reflects the low Hgb status at baseline in this disease population.

SAEs occurred in 59 (39%) patients, of which 12 were assessed as at least possible related to study drug, including bone marrow suppression, febrile neutropenia, syncope, progression to CMMoL, B-cell lymphoma, pharyngotonsilitis, pharyngitis, myalgia, sinusitis, and cerebral hemorrhage. 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 Verstovsek (2010b) for complete details on INC424 clinical study findings.

Fourteen patients discontinued study drug participation due to death, disease progression, unacceptable toxicity, or intercurrent illness. Four of 14 discontinuations were thought to be "possibly related to study drug, and included the following: (a) a 69 year-old male patient suffering from intracerebral hemorrhage without thrombocytopenia and associated death on day 374 of study drug dosed at 25 mg PO BID; (b) 71 year-old male with disease progression to CMMoL (evidence of CMMoL at screening) on day 147 of 25 mg p.o. BID; (c) 56 year old female developed grade 3 thrombocytopenia on day 278 on 50 mg p.o. BID; and (d) a 74 year-old male developed grade 3 thrombocytopenia on day 57 on 50 mg p.o. BID.

During 2 or more years of follow-up, a number of patients discontinued study drug treatment including the following: withdrawal of consent, investigators decision to discontinue

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treatment, or other reasons (n = 24); progressive disease (n = 4); toxic effects (n = 2); intercurrent illness (n = 3), and death (n = 5). A total of 17 patients died during the follow-up period of which 5 died on treatment, and 3 died within 30 days of study treatment discontinuation.

#### 1.3.4.2 Phase 1b study of INC424 in patients with MF and baseline platelet counts between 50 x $10^9$L and less than or equal to 99 x $10^9$/L

A phase Ib study of INC424 to investigate the safety of INC424 and establish the maximum safe starting dose in patients with MF who have baseline platelet counts ≥ 50,000/μL to 99,000/μL is currently ongoing (Gisslinger 2012). The (Evaluating Ruxolitinib in Patients with Low Baseline Platelet Counts Diagnosed With Myelofibrosis) study is a single-arm, open-label, dose-finding study in adult patients with PMF, PET-MF, or PPV MF. This study consists of two periods: (a) core study period (day 1 to week 24), and (b) an extension period (beyond week 24). There are two different dosing strata based on baseline platelet counts (Stratum 1: 75,000/μL to 99,000/μL starting dose is 5 mg BID; Stratum 2: 50,000/μL to 74,000/μL). A preliminary analysis based on an unplanned data cutoff date of May 16, 2012 was presented at the European Hematology Association meeting in June 2012. An updated analysis was presented at the American Society of Hematology meeting in December 2012 (Harrison 2012). The data (n=20; PMF n=14, PPV=MF n=5, PET-MF n=1) demonstrates that in this phase 1b study of INC424 in thrombocytopenic patients with MF, no DLT has occurred at the first 2 dose levels in patients with platelet counts of 50,000/μL to 99,000/μL. INC424 has been generally well tolerated, similar to the tolerability reported in the previous studies, and no patient has discontinued because of thrombocytopenia. No patient has had platelet counts below 20,000/ μL. No Grade 3/4 hemorrhagic events were reported. Treatment with INC424 led to spleen length reductions from baseline in 17 of 20 patients and three patients have experienced complete resolution of palpable splenomegaly as best response on study.

#### 1.3.4.3 Phase II study of INC424 in patients with low baseline platelet counts (50 x $10^9$/L to 100 x $10^9$/L)

A 24-week, open-label phase II study of INC424 to investigate the efficacy, hematologic effects and dose of INC424 in patients with MF, PPV-MF, and PET-MF and baseline platelet counts of 50,000 to 100,000/ μL is ongoing (INCB018424-258) (Talpaz 2012). The starting dose of INC424 is 5 mg p.o. BID with dose escalation with adequate platelet count by 5 mg once daily (i.e. 5 mg p.o. AM and 10 mg p.o.PM) every 4 weeks to a maximum of 10 mg BID. Further dose escalation requires evidence of suboptimal efficacy. An initial report with data from 41 evaluable patients was presented at the American Society of Hematology meeting in December 2012. Among patients who completed 24 weeks of treatment, most were receiving INC424 dose of 10 mg p.o. BID or higher. No patients have discontinued treatment due to adverse events. Bleeding related events were reported in 7 patients (17.1%). Grade 1 bruising events (contusion n=2 and ecchymosis n=3) were reported in 7 patients. Other bleeding events were reported in 4 patients (subdural hematoma secondary to fall, hematochezia, hemorrhoidal hemorrhage and epistaxis; all grade 1 except grade 2 hematochezia).

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#### 1.3.4.4 Phase II study of INC 424 in PV and ET patients refractory to hydroxyurea

A two-part phase 2 study was initiated to study INC424 in PV and ET patient's refractory to hydroxyurea. The first part of the study randomized patients to various doses of INC424 for determination of the optimum dose level, and the second part of the study expanded the best cohort, with allowance for dose modification to normal counts (Verstovsek 2009a).The dose levels chosen for expansion were 10 mg BID in PV patients and 25 mg BID in ET patients. A total of 34 PV and 39 ET patients were enrolled and remained on treatment for ≥ 6 months. INC424 was well tolerated in these patient populations. The most common AEs possibly related to INC424 treatment in PV patients were anemia (grade 2, 12%; no grade 3), leukopenia (grade 2, 9%; no grade 3), and thrombocytopenia (grade 2, 3%; grade 3, 3%), with ET patients most frequently demonstrating anemia (grade 2, 18%; no grade 3) and leukopenia (no grade 2; grade 3, 5%). No grade 4 toxicities were observed in this study (Verstovsek 2009a).

Rapid and sustained responses were observed in PV patients treated with INC424 (Verstovsek 2009b).Two response criteria were used to evaluate the activity of INC424 in PV patients (Table 4), both of which evaluate hematocrit, WBC counts, platelet counts, spleen size, and other symptoms (Quintas-Cardama 2009, Barosi 2009b).

The first response criteria were defined by the Department of Leukemia at the University of Texas MD Anderson Cancer Center, whereas the second was outlined by the European LeukemiaNet (Quintas-Cardama 2009, Barosi 2009b). Per criteria 1, 100% (34/34) of PV patients achieved an overall response (62% [21/34] complete response [CR], 38% [13/34] partial response [PR]), and 97% (33/34) of patients achieved normalization of hematocrit without phlebotomy. The primary reasons for not achieving CR per criteria 1 were an elevated WBC count and a palpable spleen. Per criteria 2, a 97% (33/34) overall response was observed in PV patients (45% CR, 52% PR), and 68% of patients achieved normalization of hematocrit without phlebotomy. In addition to normalization of hematocrit, WBC counts, and platelet counts and reductions in palpable spleen, reductions in constitutional symptoms, including pruritus, bone pain, and night sweats, were frequently observed (Verstovsek 2009b). Encouraging results were also noted in the ET patient population. The response criteria used were those outlined by the European LeukemiaNet (Barosi 2009b)). CR was defined as a platelet count $< 400 \times 10^9$/L, a WBC count $< 10 \times 10^9$/L, a normal spleen, and no disease-related symptoms, and PR was defined as a platelet count $< 600 \times 10^9$/L or a > 50% decrease from baseline. Per these response criteria, 90% (35/39) of ET patients achieved an overall response (13% [5/39] CR, 77% [30/39] PR). Additionally, reductions in pruritus, bone pain, night sweats, and peripheral numbness or tingling were observed (Verstovsek 2009b).

### 1.3.5 Phase III INC424 clinical trials (controlled MF study with oral JAK inhibitor treatment [COMFORT; (INCB 18424-351 and CINC424A2352)])

The results from two Phase III studies in myelofibrosis (COMFORT-I, COMFORT-II) demonstrate the effectiveness of ruxolitinib in patients with PMF, PPV-MF and PET-MF. The results of these two studies were consistent, demonstrating statistically significant ($p < 0.0001$) differences in rates of ≥35% spleen volume reduction compared with either placebo or an investigator's selection of best available therapy (BAT). Although, the time point for the

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primary endpoint (spleen volume reductions) were different in COMFORT-I (at Week 24) and COMFORT-II (at Week 28) the mean reduction in spleen volume is similar at Week 24 (31.6% vs. 29.2%, COMFORT-I and COMFORT-II, respectively).

The COMFORT-I trial is a randomized, double-blind, placebo-controlled Phase III study of the oral JAK1/JAK2 inhibitor INC424 in 309 patients with PMF, PPV MF, or PET-MF. Patients from 89 sites in the USA, Canada and Australia were randomized 1:1 to receive either INC424 (15 mg PO BID or 20 mg PO BID depending on baseline platelet count) or placebo. The primary endpoint of the study was the proportion of patients achieving ≥35% reduction in spleen volume from baseline to Week 24 as measured by MRI (or CT scan in applicable patients) and the secondary endpoints included: duration of maintenance of a ≥35% reduction from baseline in spleen volume among patients initially randomized to receive INC424, and the proportion of patients with ≥50% reduction in total symptom score from baseline to Week 24 as measured by the modified MFSAF v2.0 diary.

A total of 309 patients were enrolled in the study, with 155 randomized to INC424 and 154 to placebo. The groups were matched for baseline characteristics; the majority of patients had high-risk disease (61.2%). Patients were eligible to cross-over in this study, and 36 patients in the placebo group (23.4%) crossed over to INC424. The data cutoff date was 2-Nov-2010, the date of last patient last visit.

Significantly more patients in the INC424 group had a reduction in spleen volume (≥35%) at week 24 (41.9% vs. 0.7%; $P<.0001$). A reduction in spleen volume for ≥48 weeks was maintained in 67% patients who achieved a response on INC424. More patients receiving INC424 had an improvement of ≥50% in the total symptom score at 24 weeks compared to placebo (45.9% vs. 5.3%, $P<0.001$). Patient's receiving INC424 also had improvements in each symptom assessed on the MF-SAF. Overall survival was a secondary endpoint of COMFORT-I. Ten deaths occurred in the INC424 group vs. 14 deaths in the placebo group (hazard ratio, 0.67; 95% CI, 0.30 to 1.50; $P = 0.33$). A survival analysis based on a planned data cutoff with 4 additional months of follow-up (median follow-up, 51 weeks) revealed a significant survival advantage for patients who received INC424 (13 deaths in the INC424 group (8.4%) vs. 24 deaths in the placebo group (15.6%) (Hazard ratio, 0.50; 95% confidence interval, 0.25 to 0.98; $P = 0.04$).

INC424 was well tolerated in COMFORT-I, with most Grade 3/4 nonhematologic toxicities occurring in less than 6% patients: fatigue 5.2%, diarrhea 1.9%, dyspnea 1.3%, dizziness 0.6%, vomiting 0.6%, arthralgia 1.9%, pyrexia 0.6%, and abdominal pain 2.6% (Verstovsek 2012). Hematologic toxicity consisted primarily of anemia and thrombocytopenia. Grade 3/4 anemia occurred in 45.2% patients, Grade 3/4 thrombocytopenia occurred in 12.9% patients, and Grade 3/4 neutropenia occurred less frequently in 7.1% of patients. Approximately half of the Grade 3/4 anemia and thrombocytopenia events occur during the first 8 weeks of therapy. Treatment with INC424 enabled 41.2% to become transfusion independent. Anemia and thrombocytopenia was manageable, and thrombocytopenia generally responded to dose reduction or temporary dosing interruption. Thirteen deaths occurred in the INC424 group vs. 24 deaths in the placebo group (HR, 0.50; 95% confidence interval, 0.25 to 0.98; $P = 0.04$). The rate of discontinuation of the study drug because of AEs was 11.0% in the INC424 group vs. 10.6% in the placebo group.

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The COMFORT-II study (Study INCB 18424-352) is an open-label, randomized, active-comparator trial that compared INC424 therapy to best currently available therapy (BAT) [as determined by the investigator for each individual patient randomized to the control group] in 219 adult patients with PMF, PPV-MF or PET-MF. The control group therapy could also consist of no therapy (i.e., "watchful waiting"), or a combination of agents. COMFORT-II assessed the impact of therapy on spleen length; evaluated durability of response; and gave additional data on the long-term safety of INC424 use. Patients were randomized in a 2:1 ratio of INC424:BAT. At randomization, patients were stratified by IPSS prognostic category as having either two prognostic risk factors (intermediate-2 risk), or three or more prognostic risk factors (high risk). In COMFORT-II, the randomized treatment phase started on Study Day 1 and continued until the patient met defined criteria for disease progression. During this phase, all patients in both arms underwent an objective evaluation of spleen length using MRI or CT. The percentage of patients achieving a 35% reduction in spleen volume at 48 weeks was the primary endpoint for efficacy. MRI was the primary modality of spleen length (volume) measurement. Patients who were not candidates for MRI (including at sites where MRI is unavailable) were evaluated with sequential CT. Spleen volume was assessed by a central reader. While investigators were able to follow spleen length by palpation, results of MRI (or CT) spleen volume assessments were only to be made known to the investigator if a patient had reached a protocol-defined criterion for disease progression based upon increase in spleen volume. Patients having reached this endpoint were eligible to continue study participation in the extension phase, and if originally randomized to the control group, could cross over to receive INC424 if they met safety requirements.

The rates of leukemic-free survival, progression-free survival, overall survival, and durability of response will be determined and compared between the randomized treatment groups, using data from both the randomized treatment phase and extension phase. Additional assessments will include analysis of *JAK* mutation status, cytokine levels, and change in symptoms as assessed by the EORTC QLQ-C30 and MFSAF v 2.0 questionnaires.

In the COMFORT-II trial (Harrison 2012), 28% of the patients in the INC424 group had ≥35% reduction in spleen volume at week 48 vs. 0% in the BAT group ($P < 0.0001$); the corresponding percentages at week 24 were 32% and 0% ($P < 0.001$). The mean palpable spleen length (48 weeks) had decreased by 56% with INC424 but had increased by 4% with BAT. The median duration of response with INC424 was not reached, with 80% of patients still having a response at a median follow-up of 12 months. INC424 treatment was associated with an improvement in overall quality-of-life measures and a reduction in symptoms associated with MF. The most common hematologic abnormalities (≥ Grade 3) were thrombocytopenia and anemia, which were managed with a dose reduction, interruption of treatment, or transfusion. One patient in each group discontinued treatment due to thrombocytopenia, and none discontinued due to anemia. Non-hematologic AEs were rare and mostly grade 1 or 2. Two cases of AML were reported with the best available therapy. INC424 was also well tolerated in the COMFORT-II trial, with most Grade 3/4 non-hematologic toxicities occurring in < 3% patients: diarrhea 1%, asthenia 1%, dyspnea 1%, pyrexia 2%, nausea 1%, arthralgia 1%, fatigue 1%, pain in extremity 1%, abdominal pain 3%, headache 1%, and back pain 2%. Thrombocytopenia and anemia occurred more frequently in the patients receiving INC424 vs. BAT, although these events rarely led to treatment discontinuation (1 patient in each group discontinued the study due to thrombocytopenia) and

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were generally manageable with dose modifications, transfusions of packed red cells, or both. AEs leading to dose modification with INC424 occurred in 41% patients. Only 5% of the patients receiving INC424 required dose interruptions or reductions due to anemia and 1% due to neutropenia.

When pooling the results of COMFORT-I and COMFORT-II to examine safety of INC424, the incidence of headache was more frequent in INC424-treated patients (13.6% vs. 6.0% on placebo and 5.5% on BAT). Most AEs of headache were Grade 1 or 2. Similarly, dizziness (12.0% vs. 6.6% on placebo and 6.8% on BAT) was more frequent in INC424-treated patients, again mostly Grade 1 or 2. When adjusted for patient-year exposure, the differences were still present for headache and dizziness. Weight increase was also more frequent in INC424-treated patients than in the control groups (9.6% vs. 1.3% on placebo and 1.4% on BAT). Although some of these patients had co-reported AEs of edema, many had a past medical history of weight loss and the weight gain usually gradually accumulated over the course of one year of treatment. The majority of weight gain AEs were Grade 1 and 2. It is worth noting that weight gain may be a beneficial effect in patients with MF, given the catabolic nature of the disease and the frequency of weight loss reported as a constitutional symptom.

Other "preferred terms" with increased frequency in the INC424 arms included bruising (2.6% vs. 1.3% on placebo in [COMFORT-I, INCB 18424-351] only), contusion (8.6% vs. 5.3% on placebo and 1.4% on BAT), urinary tract infection (7.3% vs. 4.6% on placebo and 2.7% on BAT), herpes zoster (4.0% vs. 0.7% on placebo and 0% on BAT) and flatulence (3.3% vs. 1.3% on placebo and 0% on BAT). Abdominal pain was more frequent in the control groups than in the INC424 group (43% on placebo and 13.7% on BAT vs. 12% on INC424), as were weight decrease (8.6% on placebo and 8.2% on BAT vs. 1% on INC424), early satiety (8.6% on placebo and 0% on BAT vs. 0.3% on INC424) and splenic infarction (6.0% on placebo and 0% on BAT vs. 1.0% on INC424).

The most frequently occurring Grade 3 and 4 AEs regardless of study drug relationship were hematologic including anemia (14%) and thrombocytopenia (8%) (Source: [120 day safety update-Table 2.1-1.4 in Investigator Brochure]). Non-hematologic Grade 3-4 AEs were infrequent and rarely reported more frequently than in the control arms. Two patients (0.7%) had febrile neutropenia. In general, the pattern of AEs was similar between the two INC424 arms in both studies, although there were some differences in frequency for specific AEs.

In the INC424-treated Phase III population, the overall frequency of AEs leading to study drug discontinuation was 11%. This frequency was similar across both studies. None of the AEs leading to discontinuation was reported in more than two patients in any group. In the INC424-treated Phase III population, the overall frequency of AEs requiring dose reduction or interruption was 59.8%. This frequency was higher than in the control groups (placebo: 27.2%, BAT: 15.1%). The most frequently reported AEs requiring dose reduction or interruption in INC424 treated patients were thrombocytopenia (36.9%), platelet count decrease (7.6%) and anemia (5.6%). The high frequency for thrombocytopenia is due to protocol-mandated dose reductions and interruptions. Although there were no protocol specified guidelines for dose reductions secondary to anemia, some investigators chose to reduce a patient's dose in the setting of anemia to minimize this particular cytopenia. The frequency of these AEs was higher than in the control groups. All other AEs requiring dose reduction or interruption occurred with a frequency of 1.3% or less in the INC424 treated patients. There are no data

[redacted]

from the use of INC424 in pregnant women. Animal studies have shown that INC424 is embryotoxic and foetotoxic. Teratogenicity was not observed in rats or rabbits; however, the exposure margins compared to the highest clinical dose were low and the results are therefore of limited relevance for humans.The potential risk for humans is unknown. As a precautionary measure, the use of INC424 during pregnancy is contraindicated. Women of child-bearing potential should use effective contraception.

In the randomized period of the two pivotal studies in MF, COMFORT-I and COMFORT-II discontinuation due to adverse events, regardless of causality was observed in 11.3% of patients. The most frequently reported adverse drug reactions were thrombocytopenia and anemia. Hematological adverse reactions (any Common Terminology Criteria for Adverse Events [CTCAE] Grade) included anemia (82.4%), thrombocytopenia (69.8%) and neutropenia (16.6 %). Anemia, thrombocytopenia and neutropenia are dose related effects. The three most frequent non-hematological adverse reactions were bruising (21.6%), dizziness (15.3%) and headache (14.0%). The three most frequent non-hematological laboratory abnormalities were raised alanine aminotransferase (27.2%), raised aspartate aminotransferase (18.6%) and hypercholesterolemia (16.9%).

Long-term follow-up in patients with MF in the phase I/II study INCB 18424-251 and the COMFORT studies has shown that as expected, the numbers and proportions of adverse events (AEs) and serious adverse events (SAEs) have increased; however, no new safety signals have emerged. Additionally in patients with MF, the dose optimization strategy of dose reduction and occasional dose interruption for thrombocytopenia was successful in maintaining patients on therapy with only one patient on the ruxolitinib arm of each study discontinuing for thrombocytopenia; platelet transfusions occurred with low frequency, comparable to the control arms in the Phase III studies.

# 2 Rationale

## 2.1 Study rationale and purpose

The two pivotal Phase III clinical trials (COMFORT-I and COMFORT-II) evaluating INC424 are fully enrolled and published (Verstovsek 2012, Harrison 2012). Results from the COMFORT-I study (Verstovsek 2012) published in March 2012 showed a decrease in the spleen size. In addition, symptoms associated with the disease such as weight loss, pruritus, and fever were improved with the treatment. Results from the COMFORT II clinical trial also published in March 2012 (Harrison 2012), similarly demonstrated a prolonged reduction in spleen volume as well as improvement in overall QOL measures and a reduction in symptoms associated with MF. The NDA filing for INC424 with the FDA occurred on August 3rd, 2011, and FDA approval was granted on November 16th 2011.

While regulatory approval and reimbursement approval are sought, there are no means available for patients with PMF, PPV MF, or PET-MF to receive INC424 outside of a clinical trial. Implementation of an Expanded Access Program will provide an access path to INC424 for patients with PMF, PPV MF, and PET-MF, and enable collection of additional safety and efficacy data until approval by the regulatory agencies or until drug reimbursement is obtained at a country level.

[redacted]

## 2.2 Rationale for dose and regimen selected

Phase I/II trials evaluated a number of different doses and schedules of INC424. The dose that provided the best clinical outcomes coupled with the optimum safety profile was 20 mg orally BID. Among patients with baseline platelet counts from 100,000 to 200,000/ μL, a lower starting dose of 15 mg orally p.o. BID should be initiated, and in patients with platelet counts of (75,000 – <100,000/μL /μL) a starting dose of 5 mg p.o. BID should be initiated.

A more recent Phase Ib study (EXPAND) evaluating the safety and MTD of INC424 in patients with lower baseline platelet counts (75,000– 99,000/μL) was presented at the American Society of Hematology meeting in December 2012. Enrollment to date suggests that INC424 can be safely administered to patients with lower baseline platelet counts and as such patients with platelet counts of 50,000 – 99,000/μL are to be enrolled starting at a dose of INC424 of 5 mg p.o BID. A Phase II study evaluating open-label INC424 in patients with lower baseline platelet counts (50,000 – 100,000/ μL), presented at the American Society of Hematology meeting in December 2012, supports use of a starting dose of 5 mg p.o. BID (Talpaz 2012).

# 3 Objectives and endpoints

## 3.1 Primary objectives

To collect additional safety of INC424 in patients with PMF, PPV MF, or PET-MF who have either received prior treatment with commercially available agents, investigational drug or who have never received treatment.

## 3.2 Secondary objectives

- To assess the best overall response rate of INC424 in patients with PMF, PPV MF, or PET-MF, as evaluated by the investigator.
- To collect QoL information in patients with PMF, PPV MF, or PET-MF treated with INC424.
- To document MRU in patients with PMF, PPV MF, or PET-MF treated with INC424.

## 3.3 Study endpoints

### 3.3.1 Safety

- Safety and tolerability will be collected by monitoring the frequency, duration and severity of all grade AEs by the National Cancer Institute CTCAE v. 3 0, performing physical exams (PE), and evaluating changes in vital signs (VS), ECOG performance status (PS), electrocardiograms (ECGs) and serum chemistry, hematology results.
- Grade 3 and 4 AEs, Serious Adverse Events (SAEs).
- Change in laboratory values from Baseline to End of Treatment (serum chemistry and hematology).
- Changes in weight from Baseline to each assessment point and at end of treatment.
- Cardiac function as assessed by electrocardiograms (ECGs).

[redacted]

- Changes in vital signs.

### 3.3.2 Efficacy

- Best overall response to treatment as assessed by spleen palpation (calculated as the percentage change in spleen length compared with baseline).
- Change in spleen length from Baseline to end of each visit.
- Change in WBC and platelet count from Baseline will be summarized to end of treatment.
- Shift in fibrosis in the bone marrow from Baseline to worst/best value on study (where bone marrow biopsies are performed - not mandatory).
- Progression free survival (PFS), acute myeloid leukemia free survival (LFS) and overall survival (OS).
- In patients without splenomegaly, patient reported outcomes measure symptoms of the disease.

### 3.3.3 Quality of Life

(See Table 7-1 for assessments)

- Change in ECOG performance status from Baseline to each visit where the variable is measured.
- Changes in Functional Assessment of Cancer Therapy for patients with Lymphoma (FACT-Lym) version 4 from Baseline to each visit where measured (Appendix VII).
- Change in the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale from Baseline to each visit where measured (See Appendix VIII).

### 3.3.4 Medical resource utilization (MRU)

Medical resource utilization (MRU) will be assessed as follows:

- Frequency and duration of hospitalization from Baseline up to week 48 of therapy
- Frequency of emergency room visits from Baseline up to week 48 of therapy.
- Frequency of general practitioner, specialist, and urgent care visits from Baseline up to week 48 of therapy.
- Number of transfusions and transfusion dependency status end of study.
- Splenectomy and use of splenic irradiation.
- Changes in use of concomitant medications for MPN symptom management (Appendix IX).

# 4 Study design

## 4.1 Description of study design

This is a multicenter, single-arm, open-label expanded access study intended to provide additional data on the safety and efficacy of INC424 in patients with PMF, PPV MF, or PET-MF who have either previously received treatment or have not received treatment.

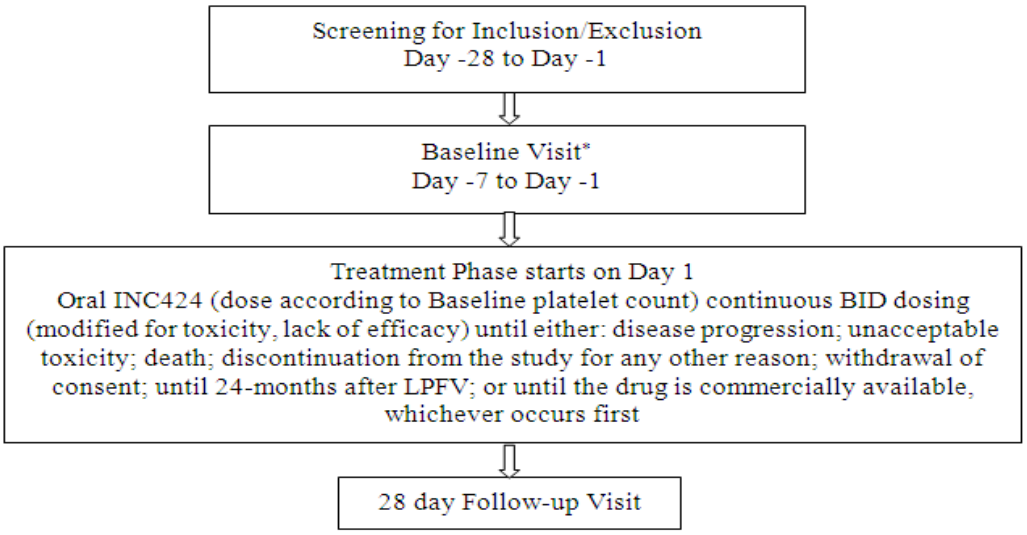
[redacted]

All patients will be treated for PMF, PPV MF, or PET-MF in each participating country with oral INC424 at a dose of 5 - 25 mg (dose based on Baseline platelet count) BID until either:

- Disease progression;
- Transplant;
- Unacceptable toxicity;
- Death;
- Discontinuation from the study for any other reason;
- Physician decision;
- Withdrawal of consent;
- Until 24-months after LPFV; or
- Until the drug is commercially available, whichever occurs first.

The FPFV occurred on 16 August 2011 and the recruitment period ended on December 31, 2014. The study enrolled a total of 2238 patients. The last patient last visit is planned for Dec 2016.

**Figure 4-1 Study design**




* Baseline evaluations should be performed within 7 days of the first dose of INC424, however platelets should be performed within a maximum of 4 days of the first dose of INC424

All patients should be screened for inclusion and exclusion criteria (Section 5.2 and Section 5.3) within 28 days prior to the first dose of INC424. See Section 7.3 for a description of the required screening evaluations. Baseline evaluations should be performed within 7 days of the first dose of INC424, however platelets should be performed within a maximum of 4 days of the first dose of INC424. See Section 7.4 for a description of the baseline evaluations required.

**Screening and eligibility:** Eligibility assessment may take place up to 28 days before the first dose of INC424 (Day -28 to Day -1). See Section 7.3 for required assessments.

[redacted]

To avoid duplication of laboratory assessments and other examinations during the 28 days before Day 1, it is permissible to use historical results provided the examinations were performed consistent with protocol requirements 7 days prior to date of first dose, however platelets should be performed within a maximum of 4 days of the first dose of INC424.

Rescreening of patients is permissible at the discretion of the investigator i.e., a patient is screened and is found to be ineligible, they may be rescreened at a later date and entered onto the study provided **all** inclusion and **no** exclusion criteria are met. Rescreening should not occur more often than every 7 days.

**Treatment period (open):** All patients who consent to study participation will start treatment with INC424 upon meeting all study eligibility criteria. The study period commences on Day 1 (day of first dose of study drug) and continues until either:

a. Disease progression;
b. Transplant;
c. Unacceptable toxicity;
d. Death;
e. Discontinuation from the study for any other reason;
f. Physician decision
g. Withdrawal of consent;
h. Until 24-months after LPFV; or
i. Until the drug becomes commercially available, whichever occurs first

Should INC424 not be available to patients after the drug is commercialized or 24-months after LPFV, Novartis will have a local transition plan in place to ensure that patients have access to INC424 without delays to treatment. Once the last dose of INC424 open label study drug is taken, or it becomes commercially available in each participating country or 24-months after LPFV, no further AEs/SAEs will be collected after the required Study Completion (see Section 7.6.3).

**End of study / treatment:** Day of last dose of open-label INC424.

**Follow-up period:** 28 days following the last dose of open-label INC424.

## 4.2 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in Section 7.6 for a prematurely 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 the IRB and/or EC of the early termination of the trial.

[redacted]

# 5 Population

## 5.1 Patient population

Adult male or female patients ≥ 18 years of age diagnosed with PMF, PPV MF, or PET-MF who have either received prior treatment with commercially available agents, investigational drug or never received treatment are eligible for this Expanded Access Study.

All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. To maximize patient safety, patients should be treated on this protocol only at centers having ready and adequate staff to care for the thrombocytopenic patient. Physicians should consider the risks and benefits of any therapy and, therefore, only enroll patients for whom the agents administered are appropriate. Although they will not be considered as formal eligibility criteria, as part of this decision-making process physicians should recognize that the following may increase the risk to the patient entering this protocol: physicians should be aware that studies show CYP3A4 is the major human CYP450 isoenzyme catalyzing biotransformation of INC424. A clinical study where a strong CYP3A4 inhibitor (ketoconazole) and INC424 was co-administered resulted in a 90% increase in AUC of INC424. Thus, INC424 dose should be adjusted when co-administration with a strong CYP3A4 inhibitor (see Section 6.2.4). Other CYP3A4 inhibitors or inducers are to be dosed with caution.

## 5.2 Inclusion criteria

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

1. Patients must give written informed consent according to local guidelines prior to any screening procedures.
2. Patients must not be eligible for another ongoing INC424 clinical trial.
3. Male or female patients aged ≥ 18 years of age.
4. Patients must be diagnosed with PMF, PPV MF or PET-MF, according to the 2008 revised International Standard Criteria Appendix I, Swerdlow 2008, Vardiman 2009, Barosi 2008), irrespective of JAK2 mutation status.
5. Patients with PMF requiring therapy must be classified as high risk (3 prognostic factors) OR intermediate risk level 2 (2 prognostic factors, no more), OR intermediate risk level 1 (1 prognostic factor, no more) with an enlarged spleen (assessment to occur at the Screening Visit).
   The prognostic factors, defined by the International Working Group (Cervantes 2009) are:
   - Age > 65 years;
   - Presence of constitutional symptoms (weight loss, fever, night sweats);
   - Marked anemia (Hgb < 10g/dL)*;
   - Leukocytosis (history of WBC > 25 x$10^9$/L);
   - Circulating blasts > 1% (in the peripheral blood).

   *A Hgb value < 10 g/dL must be demonstrated during the Screening Visit for patients who are not transfusion dependent. Patients receiving regular transfusions of packed

[redacted]

red blood cells will be considered to have Hgb < 10 g/dL for the purpose of evaluation of risk factors.

6. Patients with Intermediate-1 disease and splenomegaly must have a palpable spleen measuring 5 cm or greater from the costal margin to the point of greatest splenic protrusion.
7. Patients must have a peripheral blood blast count percentage of < 10%.
8. Patients with adequate liver function defined as total bilirubin or direct bilirubin ≤ 2.0 x ULN and ALT ≤ 2.5 x ULN.
9. Patients with adequate renal function defined as serum creatinine ≤ 2 x ULN.
10. Patients with an ECOG PS of 0, 1, or 2 (Appendix IV).
11. Women of childbearing potential must have had a negative serum pregnancy test within 14 days prior to the administration of study drug.
12. Patients must have recovered or stabilized sufficiently from any adverse drug reactions associated with prior treatment before beginning treatment with INC424.
13. Fedratinib pretreated patients with documented complete physical examination including full neurologic examination and cardiology assessment, thiamine level testing, and MRI of the brain if indicated based on signs or symptoms. Patients pretreated with fedratinib should have completed or be receiving thiamine supplementation according to the investigator's instructions.

## 5.3 Exclusion criteria

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

1. Patients eligible for hematopoietic stem cell transplantation (suitable candidate and a suitable donor is available).
2. Patients with history of malignancy in past 3 years except for treated, early-stage squamous or basal cell carcinoma in situ.
3. Patients receiving any medication listed in the "Prohibited Medications" listing (Section 6.3.3 and Appendix VI).
4. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral INC424 (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, small bowel resection).
5. Patients with cardiac disease which in the investigator's opinion may jeopardize the safety of the patient or the compliance with the protocol.
6. Patients with currently uncontrolled or unstable angina, rapid or paroxysmal atrial fibrillation or recent (approximately 6 months) myocardial infarction or acute coronary syndrome.
7. 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.
8. Patients with known active hepatitis A, B, C or who are HIV-positive.
9. Patients with inadequate bone marrow reserve at the Baseline visit as demonstrated by:
   - ANC ≤ 1000/μL.

[redacted]

- Platelet count <50,000/μL without the assistance of growth factors, thrombopoietic factors or platelet transfusions.

10. Patients with any history of platelet counts < 50,000/μL or ANC < 500/μL except during treatment for a MPD or treatment with cytotoxic therapy for any other reason.
11. Patients with coagulation parameters (PT, PTT, or INR) >1.5 x ULN.
12. Patients with known hypersensitivity to INC424 or other JAK1/2 inhibitors, or to their excipients.
13. Patients under ongoing treatment with another investigational medication or having been treated with an investigational medication within 30 days of screening or with fedratinib within 14 days of screening.
14. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test (> 5 mIU/mL).
15. 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 28 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), total 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). The vasectomized male partner should be the sole partner for that subject.
    - Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

    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), total 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.
16. Patients who are unable to comprehend or are unwilling to sign an ICF
17. Patients with active alcohol or drug addiction that would interfere with their ability to comply with the study requirements
18. Patients with any concurrent condition that, in the Investigator's opinion would jeopardize the safety of the patient or compliance with the protocol.

[redacted]

19. In the case of ruxolitinib pretreated patients, ruxolitinib primary resistant patients defined as:
    - No spleen reduction within the first 12 weeks after front line therapy with ruxolitinib. AND
    - No reduction in symptoms within the first 12 weeks after first-line treatment with ruxolitinib.
20. In the case of ruxolitinib pretreated patients, patients discontinuing ruxolitinib due to a Grade 4 AE related or suspected to be related to ruxolitinib.

# 6 Treatment

## 6.1 Investigational treatment, other study treatment, supportive treatment

### 6.1.1 Study drug dosing

All eligible patients with PMF, PPV MF, or PET MF who consent to participate in this study will receive INC424 open-label investigational drug provided free of charge by Novartis Pharmaceuticals at a dose of 5 – 25 mg BID [dose based on Baseline platelet count] until either:

- Disease progression;
- Transplant;
- Unacceptable toxicity;
- Death;
- Discontinuation from the study for any other reason;
- Physician decision
- Withdrawal of informed consent;
- Until 24-months after LPFV; or
- Until the drug is commercially available, whichever occurs first.

The starting dose of INC424 will be determined based on baseline platelet counts as follows:

- Patients with a baseline platelet count of > 200,000/μL will begin dosing at 20 mg PO BID.
- Patients with a baseline platelet count of between 100,000/μL – 200,000/μL (inclusive) will begin dosing at 15 mg PO BID.
- Patients with a Baseline platelet count of 50,000/ μL – <100,000/μL /μL will begin dosing at 5 mg BID (one 5 mg tablet BID)
- Patients with platelet counts less than 50,000/μL are ineligible for the study (see Section 5.2 and Section 5.3).

**Dosage Tablet Combinations for Patients**

| For 25 mg PO BID | For 20 mg PO BID | For 15 mg PO BID | For 10 mg PO BID | For 5 mg PO BID |
|---|---|---|---|---|
| Two 10 mg tablets | Four 5 mg tablets | One 10 mg tablet and | One 10 mg tablet | One 5 mg tablet |

[redacted]

| For 25 mg PO BID | For 20 mg PO BID | For 15 mg PO BID | For 10 mg PO BID | For 5 mg PO BID |
|---|---|---|---|---|
| and one 5mg tablet | | one 5 mg tablet | | |
| One 10 mg tablet and three 5 mg tablets | Two 10 mg tablets | Three 5mg tablets | Two 5 mg tablets | |
| Five 5 mg tablets | Two 5 mg tablets and one 10 mg tablet | | | |

INC424 tablets will be administered orally without regards to food in an outpatient setting in accordance with the specified dosing schedules. The dosage strength is 5 mg or 10 mg per tablet INC424. INC424 tablets are to be taken orally BID, approximately 12 hours apart (morning and night). INC424 will be self-administered by the patient, and each investigator should instruct the patient to take the study drug as per protocol (if applicable). All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record (DAR) eCRF.

A standardized approach is to be taken for dosing adjustments and for safety and efficacy so that each patient is titrated to their most appropriate doses (see Section 6.2). Doses of INC424 are not to exceed 25 mg PO BID

**Table 6-1 Dose and treatment schedule**

| Study drugs | Pharmaceutical form and route of administration | Dose | Frequency |
|---|---|---|---|
| INC424 | Tablet for oral use | See Section 6.1.1. | BID continuously |

## 6.2 Dose modifications

### 6.2.1 Dose increases of INC424

#### 6.2.1.1 Dose modification for patients starting INC424 at a dose of 15 – 20 mg BID

##### 6.2.1.1.1 Dose increases of INC424 at week 4

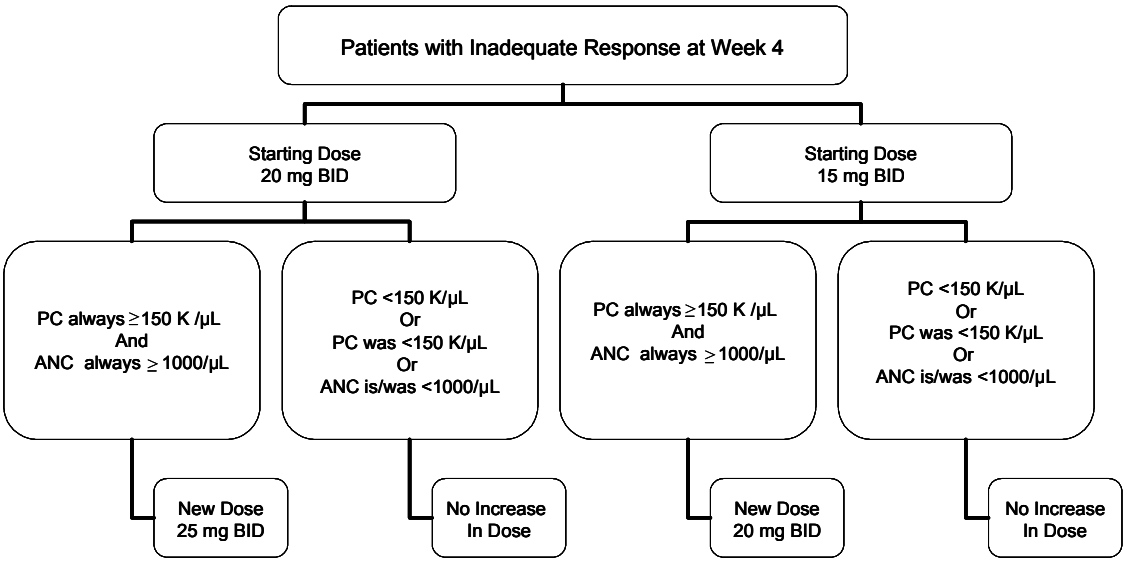
As indicated in Section 6.1.1 Study Drug Dosing, the initial dose of INC424 will be determined by the Baseline platelet count. In order to optimize each patient's dosage, after the first 4 weeks of therapy, doses may be increased by 5 mg BID for patients who meet all of the following conditions:

- Palpable spleen length below the costal margin that has been reduced by LESS THAN 40% at Week 4 visit relative to Baseline.
- Platelet count at the Week 4 blood draw is > 150,000/μL and platelet count has never been below 150,000/μL at a prior laboratory evaluation while receiving INC424. (See Figure 6-1).

Absolute neutrophil count (ANC) levels have remained at or above 1000/μL since enrollment in the study.

[redacted]

**Figure 6-1 Dose increase strategies for patients starting on INC424 15 – 20 mg BID with inadequate responses after at least Week 4:**




#### 6.2.1.1.2 Dose increases beyond week 4

After Week 4 (month 1), dose increases of INC424 are allowed for those patients who exhibit an INCREASE in palpable spleen length. The rules for these optional dose increases are as follows:

- The dose increases may only occur if the platelet count and ANC data for that visit are available.
- The palpable spleen length for that Study Visit must show a 2 cm or greater INCREASE in length compared to the on-study nadir (lowest palpable spleen measurement during the study, including Baseline).
- The patient must NOT have had a prior safety-related dose reduction.
- The following platelet threshold have been met:
  - The patient must have had a platelet count ≥150,000/µL at every assessment since Baseline for those starting INC424 at a starting dose of 15 – 20 mg BID.
- The patient must have had ANC ≥1000/µL at every assessment since baseline.
- The dose increase may only be an increase of 5 mg BID.
- The total dose may never exceed 25 mg BID.
- Following a dose increase, platelet count and ANC levels should be assessed approximately 2 weeks after the dose adjustment. If a regularly scheduled Study Visit does not coincide with this required blood draw, an unscheduled Interim Visit should be held to collect samples for hematology.

Dose adjustments for safety (Section 6.2.2), and reinstitution of doses (Section 6.2.3) will apply whether the patient is on the original dose, or a dose that was increased for lack of efficacy.

[redacted]

### 6.2.1.2 Dose modification for patients starting INC424 at a dose of 5 mg BID

#### 6.2.1.2.1 Dose increases at week 4

For those patients who start INC424 treatment at a dose of 5 mg BID, dose increases can be made as described below. The dose can be escalated 5 mg once a day starting at week 4, and thereafter no more than every two weeks ONLY if:

- Inadequate efficacy is seen with the current dose level (See Section 6.2.1.1.1)
- No treatment-related toxicity has occurred with the current dose level, resulting in treatment reduction or interruption or discontinuation in the previous 28 days
- The minimum platelet count at the time of the escalation is ≥ 50,000/μL
- ANC > 1000/μL since last scheduled visit
- The total dose may never exceed 25 mg BID

If the above criteria are met, then the INC424 dose can be increased by 5 mg o.d. e.g., from 5 mg BID to 5 mg QAM and 10 mg QPM.

#### 6.2.1.2.2 Dose increases beyond week 4

After Week 4, dose increases of INC424 are allowed for those patients who exhibit an INCREASE in palpable spleen length. The rules for these optional dose increases are as follows:

- The dose increases may only occur if the platelet count and ANC data for that visit are available.
- The palpable spleen length for that Study Visit must show a 2 cm or greater INCREASE in length compared to the on-study nadir (lowest palpable spleen measurement during the study, including Baseline).
- The patient must NOT have had a prior safety-related dose reduction.
- The following platelet threshold have been met:
  - The patient must have had a platelet count ≥50,000/μL at every assessment since Baseline for those starting INC424 at a starting dose of 5 mg BID
- The patient must have had ANC ≥1000/μL at every assessment since baseline.
- The dose increase may only be an increase of 5 mg once daily for those starting on an INC424 dose of 5 mg BID.
- The total dose may never exceed 25 mg BID.
- Following a dose increase, platelet count and ANC levels should be assessed approximately 2 weeks after the dose adjustment. If a regularly scheduled Study Visit does not coincide with this required blood draw, an unscheduled Interim Visit should be held to collect samples for hematology.

Dose adjustments for safety (Section 6.2.2), and reinstitution of doses (Section 6.2.3) will apply whether the patient is on the original dose, or a dose that was increased for lack of efficacy.

[redacted]

### 6.2.2 Dose interruption or dose reduction

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. The following guidelines need to be applied: for all patients who are receiving INC424, there are mandatory dose decreases or dose interruptions for declining platelet counts or ANC levels that might be observed while on INC424 therapy. In addition to mandatory dose interruption or decrease for hematologic toxicities, there are mandatory criteria for permanent discontinuation of INC424 (See Section 6.2.6).

Dosing must be held if platelet counts decline below 50,000/µL (Grade 3 laboratory abnormality by CTCAE v. 3.0, or if ANC falls below 500/µL while receiving INC424.

#### 6.2.2.1 Dose interruption or dose reduction for patients starting INC424 at doses of 15 – 20 mg p.o. BID

Doses should be decreased for platelet count values < 125,000/µL as shown in Table 6-2 with optional restarting or resuming prior dose after recovery (Section 6.2.3). In order to provide sufficient data to make the dose adjustment decisions, it is recommended that hematology parameters be obtained at least weekly for platelet count <100,000/µL or ANC < 1000/µL and at least two times weekly for platelet count < 50,000/µL or ANC < 500/µL.

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

**Table 6-2 Dose reductions in INC424 for safety in patients with platelet count declines (for those starting on INC424 dose of 15 – 20 mg p.o. BID)**

| Platelet Count at Time of Decline | Dose at the Time of Platelet Decline | | | | |
|---|---|---|---|---|---|
| | 25 mg BID | 20 mg BID | 15 mg BID | 10 mg BID | 5 mg BID |
| | Dose that MUST be Instituted | | | | |
| ≥ 125,000/µL | No dose reduction required | | | | |
| 100,000/µL to < 125,000/µL | 20 mg BID | 20 mg BID | 15 mg BID | 10 mg BID | 5 mg BID |
| 75,000/µL to < 100,000/µL | 10 mg BID | 10 mg BID | 10 mg BID | 10 mg BID | 5 mg BID |
| 50,000/µL to < 75,000/µL | 5 mg BID | 5 mg BID | 5 mg BID | 5 mg BID | 5 mg BID |
| < 50,000/µL | Stop Dosing | | | | |

#### 6.2.2.2 Dose interruption or dose reduction for patients starting INC424 at doses of 5 mg p.o. BID

**D**ose modifications are made according to the platelet count as follows (see Table 6-3):

- If platelets > 25,000 - < 50,000/µL: reduce the INC424 dose by 5 mg o.d.
- If platelets ≤ 25,000/µL: hold treatment. Treatment can be restarted at a later date if platelets increase to ≥ 50,000/µL.

The patients should then be reassessed the following month. If the platelet count improves, the patient can restart treatment, and if the platelet count does not improve the patient should be withdrawn from the study.

[redacted]

These changes must be recorded on the DAR eCRF.

**Table 6-3 Dose reductions in INC424 for safety in patients with platelet count declines (for those starting on INC424 dose of 5 mg PO BID)**

| Platelet count at time of decline | Dose reduction/hold |
|---|---|
| ≥50,000/μL | No dose reduction required |
| < 50,000/μL and > 25,000/μL | Decrease dose by 5 mg OD |
| ≤25,000/μL | Hold treatment; treatment may be restarted once the platelet count increases to >50,000/μL as outlined in Section 6.2.3.2 |

Study drug MAY be permanently discontinued for a Grade 4 clinical event that has NOT been confirmed upon rechallenge with the study drug, at the option of the Investigator.

### 6.2.2.3 Dose modification for renal impairment

No specific dose adjustment is needed in patients with mild or moderate renal impairment.

In patients with severe renal impairment (creatinine clearance less than 30 mL/min) the recommended starting dose based on platelet count should be reduced by approximately 50% BID (15mg BID or 25mg BID should have the higher dosage taken in the morning). Patients diagnosed with severe renal impairment while receiving ruxolitinib should be carefully monitored and need to have their doses reduced to avoid adverse drug reactions.

There are limited data to determine the best dosing options for patients with end-stage renal disease on hemodialysis. Available data in this population suggest that the starting dose for patients with end-stage renal disease on hemodialysis is 15 mg INC424 for patients with platelet count between 100,000-200,000/μL or 20 mg for patients with platelet count of >200,000/μL. Subsequent doses (single administration) should be administered on hemodialysis days following each dialysis session. Additional dose modification should be made with careful monitoring of safety and efficacy. No data is available for dosing patients who are undergoing peritoneal dialysis or continuous venovenous hemofiltration. No data is available for patients who have lower platelet counts and renal failure.

### 6.2.2.4 Dose modification for hepatic impairment

Patients diagnosed with hepatic impairment while receiving ruxolitinib should be carefully monitored and may need to have their dose reduced to avoid adverse drug reactions.

In patients with any hepatic impairment the recommended starting dose based on platelet count should be reduced by approximately 50% BID (15mg BID or 25mg BID should have the higher dosage taken in the morning). Subsequent doses should be adjusted based on careful monitoring of safety and efficacy. Patients diagnosed with hepatic impairment while receiving INC424 should have complete blood counts, including a white blood cell count differential (neutrophils, lymphocytes, eosinophils, basophils, monocytes, and blast cells), monitored at least every one to two weeks for the first 6 weeks after initiation of therapy with INC424 and as clinically indicated thereafter once their liver function and blood counts have been stabilized. INC424 dose can be titrated to reduce the risk of cytopenia.

[redacted]

### 6.2.3 Restarting or reinstituting previous dose

#### 6.2.3.1 Restarting or reinstituting previous dose for patients who start INC424 15 – 20 mg BID

Dosing of INC424 may be restarted or increased following recovery of platelet counts and/or ANC to acceptable levels as illustrated in Table 6-4 for those patients who start on INC424 15 – 20 mg BID. The objective for restarting or escalating after a reduction for safety is to find the highest safe dose of INC424 for each patient, with increases in dose generally not more than in increments of 5 mg BID and not more often than every 2 weeks. Patients who are restarting after a reduction for thrombocytopenia may not receive doses above 20 mg BID maximum. Similarly, ANC levels that decline to < 500/µL necessitate immediate dose interruption (Section 6.2.6). ANC level recovery to 500 /µL and above but less than 750/µL will allow dosing to be restarted at 5 mg BID, and ANC levels between 750/µL, but < 1000/µL may restart at 10 mg BID. Absolute neutrophil count level increases to above 1000/µL will allow a further dose increase to a maximum of 20mg BID.

The maximum dose used should never exceed 5mg BID LESS than any dose that resulted in platelets falling below 100,000/µL or ANC falling below 500/µL. After restarting using the guidelines in Table 6-4, if it is found that a patient cannot tolerate the lowest allowed dose (5mg BID, or 5mg QD with concomitant CYP3A4 inhibitor, see Section 6.2.4) without platelets falling below 50,000/µL, neutrophils falling below 500/µL, or Hgb falling below 6.5g/dL despite the use of transfusion therapy, drug must be permanently discontinued (Section 6.2.6, and Section 7.6.1).

**Table 6-4 Restarting or increasing INC424 dose after safety interruptions or dose reductions for patients starting on doses of 15 – 20 mg BID**

| **Current Platelet Count** | **Dose Restart or Dose Increase Guidelines** |
|---|---|
| < 50,000/µL | Continue hold |
| 50,000/µL to < 75,000/µL | 5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID |
| 75,000/µL to < 100,000/µL | 10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID |
| 100,000/µL to < 125,000/µL | 15 mg BID |
| ≥125,000/µL | 20 mg BID |
| **Current ANC Level** | **Dose Restart or Dose Increase Guidelines** |
| < 500/µL | Continue hold |
| 500 to < 750/µL | 5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID |
| 750 to < 1000/µL | 10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID |
| 1000 to < 1500/µL | 15 mg BID for at least 2 weeks; if stable may increase to 20 mg BID |
| ≥1500/µL | 20 mg BID |

**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.

[redacted]

#### 6.2.3.2 Restarting or reinstituting previous dose for patients who start INC424 at 5 mg BID

Dosing of INC424 may be restarted or increased following recovery of the platelet count to ≥ 50,000/µL. Reinitiate treatment at a dose of 5 mg o.d. The dose may be increased by 5 mg o.d. every two weeks based on platelet counts and the absence of other adverse events.

When the ANC is < 500/µL, hold INC424 dosing. INC424 can be reinitiated in this population once the ANC is ≥ 500/µL, at a dose of 5 mg o.d. The dose may be increased by 5 mg o.d. every two weeks based on platelet counts and the absence of other adverse events.

### 6.2.4 Dose reductions for concomitant CYP inhibitor usage

INC424 is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isoenzymes. With concomitant dosing of strong (potent) CYP inhibitors such as oral ketoconazole, plasma exposure of INC424 increases approximately 2-fold. Thus, a dose reduction of ~ 50% for INC424 is appropriate for patients who take ketoconazole or other potent CYP3A4 inhibitors as concomitant medication. Twice daily (BID) doses will be decreased to the corresponding once daily dose as follows:

- If dose is 25 mg BID, change dose to 25 mg **QD**
- If dose is 20 mg BID, change dose to 20 mg **QD**
- If dose is 15 mg BID, change dose to 15 mg **QD**
- If dose is 10 mg BID, change dose to 10 mg **QD**
- If dose is 5 mg BID, change dose to 5 mg **QD**

If a patient is already on a once daily dose of INC424, and a potent CYP3A4 inhibitor is added as a concomitant medication, the dose should be reduced to 5 mg every other day.

More frequent monitoring of hematology parameters and clinical signs and symptoms of ruxolitinib related adverse reactions is recommended upon initiation of a strong (potent) CYP3A4 inhibitor.

Potent inhibitors of CYP3A4 include oral ketoconazole, clarithromycin, itraconazole, voriconazole, nefazodone, telithromycin (Flockhart 2007). Based on the very low overall bioavailability of topical ketoconazole, no dosage adjustment is needed for use with topical ketoconazole. NOTE: once the course of therapy using a CYP 3A4 inhibitor has been completed, the patient should resume their prior BID dose regimen of INC424 beginning the next day.

### 6.2.5 Optional dose tapering strategy in the event of study drug discontinuation

Following interruption or discontinuation of ruxolitinib, symptoms of myelofibrosis may return over a period of approximately one week. There have been cases of patients discontinuing ruxolitinib who sustained more severe events, particularly in the presence of acute intercurrent illness. It has not been established whether abrupt discontinuation of ruxolitinib contributed to these events. Unless abrupt discontinuation is required, gradual tapering of the dose of ruxolitinib may be considered, although the utility of the tapering is unproven.

[redacted]

When a decision is made to permanently discontinue INC424 therapy for reasons other than low platelet counts or ANC levels, 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. 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 adverse drug reactions of discontinuation. Short-term courses of corticosteroids have been used to moderate the withdrawal of INC424 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 until the end of INC424 administration and in the event of an AE through resolution of the AE.

### 6.2.6 Dose interruption and discontinuation of study drug

In some circumstances, it may be necessary to temporarily interrupt treatment as a result of adverse drug reaction that may have an unclear relationship to study drug. Except in cases of emergency or for protocol mandated holds for ANC or platelet count, it is recommended that the investigator consult with the Sponsor medical monitor (or other representative of the Sponsor) before temporarily interrupting therapy. Study drug may be held by the investigator at any time if there is concern about patient safety, and for all aspects of the conduct of the protocol the safety of the individual patient is paramount. Treating investigators may employ any means necessary to ensure patient safety, particularly in medical circumstances not anticipated by this protocol. Additionally, the investigator must obtain approval from the Sponsor before restarting study drugs that were temporarily discontinued for an adverse experience.

Dosing must be halted immediately if any of the following occur for patients starting with 15 & 20 mg BID:

- Platelet counts fall below 50,000/μL
- ANC levels fall below 500/μL
- Hemoglobin cannot be maintained ≥6.5 g/dL despite the use of transfusion therapy

Dosing may be reinstated following dose holding using the re-start schema detailed in Section 6.2.3. In order to provide sufficient data to make the dose adjustment decisions, it is recommended that hematology parameters be obtained at least weekly for platelet count < 100,000/μL or ANC < 1000/μL and at least two times weekly for platelet count < 50,000/μL or ANC < 500/μL. (Note: patients with platelet counts of < 10,000/μL should be hospitalized, unless local or national practice does not permit it).

If a patient on a dose-hold requires frequent testing for safety parameters, these tests may be performed at a local laboratory. If the study drug is interrupted for any reason for more than 8 weeks, dosing may not be restarted, except in the case of splenectomy, for which a maximum 12 week period of study drug interruption is permitted. Although study guidelines provide for dose reduction/interruption for the management of hematologic or non-hematologic toxicities that occur during the course of the study, the following guidelines should be used to determine whether permanent discontinuation of study drug is necessary.

[redacted]

Discontinuation of study drug for **hematologic toxicity**:

Study drug MUST be permanently discontinued if the lowest allowed dose (5 mg BID or 5 mg QD with concomitant CYP3A4 inhibitor) is not tolerated due to the following:

- Platelets cannot be maintained ≥ 50,000/μL.
- Absolute neutrophil count cannot be maintained ≥500/μL.
- Hemoglobin cannot be maintained ≥6.5 g/dL despite the use of transfusion therapy.

In the event that any patient permanently discontinues the study drug, regardless of reason, reasonable efforts should be made to have the patient return for an early termination visit and have the End of Treatment evaluations completed as described in Section 7.6 and Section 7.6.2. The site is requested to provide voluntary follow-up of all withdrawn patients, with regard to incidence of leukemia or death.

The date the patient discontinued the study drug and the specific reason for discontinuation will be recorded in the eCRF. This will include reasons such as discontinued due to disease worsening or withdrawn due to adverse event. This information will be used to summarize the reasons for study withdrawal.

#### 6.2.6.1 Dose reduction for non-hematological safety

Study drug MUST be permanently discontinued upon the occurrence of a clinically significant Grade 3 or Grade 4 laboratory or non-laboratory abnormality attributed to ruxolitinib if fails to resolve to Grade 2 or better within 8 weeks or if a lower re-start dose or administration schedule is either not available or likely to be clinically ineffective.

Although study guidelines provide for dose reduction/interruption for the management of hematologic or non-hematologic toxicities that occur during the course of the study, the investigator should determine whether permanent discontinuation of study drug is necessary.

### 6.2.7 Treatment of investigational drug overdose

There is no known antidote for INC424 overdose. Overdose will be defined as the use of INC424 in doses in excess of that specified in the protocol. . Patients overdosed should be treated with appropriate supportive care until recovery. Use of INC424 in doses in excess of that specified in the protocol should not be recorded in the eCRFs as an AE of 'Overdose'. An overdose with associated SAEs should be recorded as the SAE diagnosis/symptoms on the relevant AE and SAE forms in the eCRFs. An overdose with associated non-serious AEs should be recorded as the AE diagnosis/symptoms on the relevant AE forms in the eCRFs. An overdose without associated symptoms should not be recorded as an AE in the eCRFs.

## 6.3 Concomitant medications

All concomitant medications and treatments must be recorded on the appropriate eCRF. Any prior medication received up to 30 days prior to the first dose of study drug will be recorded in the CRF. All prior medications used to treat (record applicable indication) disease will be recorded. Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without consultation with the investigator.

[redacted]

### 6.3.1 Permitted concomitant therapy

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications or the Procedures and Significant Non-Drug Therapies eCRF, respectively.

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without consultation with the investigator. At each visit, the patient must be asked about any new medications he/she is or has taken.

All medications taken ≤ 30 days prior to study entry should be recorded on the Concomitant Medications Prior to Start of Study Drug Case Report Form (eCRF). All prior medications used to treat PMF, PPV MF, or PET-MF will be recorded. All concomitant treatments during the trial will also be recorded in the eCRF.

The following restrictions apply during the study:

- No other investigational therapy should be given to patients.
- No anticancer agents other than the study medication (INC424) should be given to patients until disease progression or withdrawal from the study. If such agents are required for a patient then the patient must first be withdrawn from the study.

### 6.3.2 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:

- In patients for whom warfarin or heparin use will be initiated, the degree of thrombocytopenia should be considered, coagulation parameters monitored, and dose of anticoagulant adjusted accordingly. If anticoagulation is required during INC424 administration, low molecular weight heparin is preferred, particularly in patients who are: elderly, history of CHF, diabetic, hepatic or renal disease, or atrial fibrillation (first episode).
- Low dose aspirin (≤150 mg/day) and non-steroidal anti-inflammatory agents (acetaminophen, ibuprofen) may be used. Aspirin doses > 150 mg are prohibited.
- Inducers or inhibitors of the metabolizing enzyme CYP3A4 (Appendix VI):
- When concomitant administration of a strong (potent) inhibitor of CYP3A4 metabolizing enzymes or dual CYP2C9/CYP3A4 inhibitors (Appendix VI) is required for patient management, the dose of INC424 tablets must be reduced by approximately 50% to be administered twice daily by decreasing the twice daily dose or by decreasing the frequency of dosing to the corresponding once daily dose when twice daily dose is not practical." (See Section 6.2.4).
    - Note: No dose adjustment of ruxolitinib is needed for use with topical ketoconazole. Note: More frequent monitoring of hematology parameters and clinical signs and symptoms of ruxolitinib realted adverse reacstions is recommended upon initiation of a string (potent) CYP3A4 inhibitor

[redacted]

- No dose adjustment will be made when moderate systemic CYP3A4 inducers (Appendix VI) are co-administered with study treatment.
- Granulocyte growth factors are not allowed while study treatment is being administered but may be used for severe neutropenia at the Investigator's discretion while study medication is being withheld.
- Certain herbal supplements see Appendix VI are prohibited. Because the composition, pharmacokinetics and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is strongly discouraged during the study however if used during the trial please ensure the treatment is entered on the proper eCRF page (see Section 6.3.1).

### 6.3.3 Prohibited concomitant therapy

The following medications are prohibited during the study until treatment discontinuation:

- 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 until treatment discontinuation is prohibited.
- Use of hydroxyurea, interferon, thalidomide, busulfan, lenalidomide, or anagrelide is not permitted at any time during participation in the study. These medications should be discontinued prior to Day 1 of INC424 therapy. All adverse events attributed to these medications should be resolved prior to Day 1 of INC424 treatment.
- Potent inducers of CYP3A4 Appendix VI are not permitted.
- Aspirin in doses exceeding 150 mg per day is prohibited.

## 6.4 Patient numbering, treatment assignment and randomization

### 6.4.1 Patient numbering

Each patient is identified in the study by a Patient Number (Patient No.), that is assigned when the patient is first enrolled for screening and is retained as the primary identifier for the patient throughout his/her entire participation in the trial. The Patient No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential patient number suffixed to it, so that each patient is numbered uniquely across the entire database. Upon signing the informed consent form, the patient is assigned to the next sequential Patient No. available to the investigator through the Oracle Clinical RDC interface.. Once assigned, the Patient No. must not be reused for any other patient and the Patient No. for that individual must not be changed, even if the patient is re-screened.

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

Patient numbering for those patients who may have participate in CINC424A2401 before being under fedratinib: those patients will receive a new patient number as per process described above.

[redacted]

### 6.4.2 Treatment assignment and randomization

The investigational treatment (INC424) will be provided to all participants and no randomization processes will apply.

### 6.4.3 Treatment blinding

All study participants will receive active medication, therefore blinding is not applicable.

## 6.5 Study drug supply

### 6.5.1 Study drug preparation and dispensation

Study drug refers to open label INC424 (ruxolitinib). All dosages prescribed to the patient and all dose changes during the study must be recorded on the DAR form.

### 6.5.2 Study drug packaging and labeling

INC424 investigational drug is provided as 5 mg and 10mg tablets. INC424 5 mg and 10mg tablets are packaged in bottles or in blisters according to local Heath Authority requirements. Medication labels will be in the local language and comply with the legal requirements of each country. They will include the patient number, but no information about the patient.

Patients will initially receive a 4-week supply of INC424 each month for the first 3 months of the study. Once the study visits expand to every 3 months, patients will have a 3-month supply of INC424 dispensed. Immediately before dispensing the study drug to the patient, the investigator or his/her designee will detach the outer part of the label from the packaging and affix it to the source document containing the patients' unique patient number (identifier).

INC424 treatment will be administered until either:

- Disease progression;
- Transplant;
- Unacceptable toxicity;
- Death;
- Discontinuation from the study for any other reason;
- Physician decision
- Withdrawal of consent;
- Until 24-months after LPFV; or
- Until the drug is commercially available, whichever occurs first

Should INC424 not be available to patients after the drug is commercialized or 24-months after LPFV, Novartis will have a local transition plan in place to ensure that patients have access to INC424 without delays to treatment.

### 6.5.3 Drug supply and storage

Study treatments 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

[redacted]

designated assistants have access. Upon receipt, INC424 should be stored according to the instructions specified on the drug labels. Details are listed in Table 6-5.

**Table 6-5 Supply and storage of study treatments**

| Study treatments | Supply | Storage |
|---|---|---|
| INC424 | Centrally and/or locally supplied by Novartis | Refer to study treatment label and/or to local treatment label |

Under normal conditions of handling and administration, INC424 is not expected to pose significant safety risks to site staff. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis Pharmaceuticals upon request.

Investigational product must be kept in an appropriate, secure area and stored in accordance with the physical conditions specified on the INC424 label. Patients should be carefully instructed regarding INC424 storage conditions when they receive their 4-week or 12-week supplies of investigational product. All drug supplies are to be used only for this protocol and not for any other purpose. Patients should be advised to keep the INC424 in a locked cupboard away from children where possible.

Access to, and administration of, the investigational product will be limited to the investigator and authorized staff. Investigational product must be dispensed or administered only to patients enrolled in the study in accordance with the protocol and not for any other purpose.

### 6.5.4 Study drug compliance and accountability

#### 6.5.4.1 Study drug compliance

Patients will be requested to bring any unused medication (if applicable), including empty packaging to the clinic at each visit. Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

- All doses taken by the patient and all dose changes or interruptions during the study must be recorded on the DAR eCRF.
- The investigator or his/her designee must keep documentation (overall drug accountability for the study as well as individual study drug accountability for each patient) of tablets administered, tablets used, dose changes, and dates dispensed.
- Drug accountability will be monitored by the field monitor during site visits and at the completion of the study.

In the absence of safety concerns, the patient may be dispensed up to an 84-day supply of medication at the investigator's discretion

#### 6.5.4.2 Study drug accountability

The investigator or designee must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability ledger. Drug accountability will be noted by the

[redacted]

field monitor during site visits and at the completion of the study. Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.

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

#### 6.5.4.3 Disposal and destruction

The drug supply can be destroyed at the local Novartis facility, Drug Supply group or third party, as appropriate.

The drug supply may be destroyed at the site only if permitted by local regulations and authorized by Novartis.

# 7 Visit schedule and assessments

## 7.1 Study flow and visit schedule

Table 7-1 lists all of the assessments except for laboratory assessments and indicates with an "X" the visits when they are performed. Table 7-2 lists all laboratory assessments. All data obtained from these assessments must be supported in the patient's source documentation. The table indicates which data are entered into the database (D) or remain in source documents only (S). Assessments that generate data for database entry and which are recorded in eCRFs are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g., laboratory data) are listed by test name.

Study assessments and procedures are outlined in Section 7.4. Baseline assessments, and in Section 7.5 (On treatment assessment). Please refer to Table 7-1. Visit Evaluation Schedule, for timing of assessment.

[redacted]

**Table 7-1 Visit evaluation schedule**

| Evaluation | Reference to Section | Screening | Baseline | Day 1 | Week 4# | Week 8# | Week 12# | Week 24# | Week 36 | Week 48 | Week 60 & q12w onwards | End of Study/End of Treatment Section 7.6.2 | Follow-up / Study Completion Evaluation Section 7.6.3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit name** | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | | | |
| **Day of visit** | | **-28 to -1** | **-7 to -1** | **Day 1** | **Day 28** | **Day 56** | **Day 84** | **Day 168** | **Day 252** | **Day 336** | | | |
| Eligibility checklist(s) | 7.3 | | | | | | | | | | | | |
| Written Informed Consent (D) | 12.3 | X | | | | | | | | | | | |
| Patient Demographics (D) | 11.3 | X | | | | | | | | | | | |
| Inclusion / exclusion criteria (D) | 5.2/5.3 | X | X | | | | | | | | | | |
| Relevant medical history/ current conditions (D) | 7.3 | X | | | | | | | | | | | |
| MRI if clinically indicated (S) | 7.3 | X | | | | | | | | | | | |
| Diagnosis of PMF, PPV MF, and PET-MF(D) includes bone marrow biopsy with grading of fibrosis (if available) | Appendix I | X | | | | | | | | | | | |
| Prior and current concomitant medications/significant non-drug therapies (D) | 7.3 | X | X | X | X | X | X | X | X | X | X | X | X |
| History of disease (D) | 7.3 | X | X | | | | | | | | | | |
| Treatment History (D) | 7.3 | X | X | | | | | | | | | | |
| Disease status documentation (low, intermediate-1, intermediate-2, high risk) (D) | 7.3 | X | | | | | | | | | | | |
| Transfusion history (S)(D) | 7.4 | X | X | X | X | X | X | X | X | X | X | X | X |
| Physical examination (S) | 7.4/8.2.3 | X | X | | X | X | X | X | X | X | X | X | X |

[redacted]

| Evaluation | Reference to Section | Screening | Baseline | Day 1 | Week 4# | Week 8# | Week 12# | Week 24# | Week 36 | Week 48 | Week 60 & q12w onwards | End of Study/End of Treatment Section 7.6.2 | Follow-up / Study Completion Evaluation Section 7.6.3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit name** | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | | | |
| **Day of visit** | | **-28 to -1** | **-7 to -1** | **Day 1** | **Day 28** | **Day 56** | **Day 84** | **Day 168** | **Day 252** | **Day 336** | | | |
| Vital signs (D) | 7.4/8.2.4 | X | X | | X | X | X | X | X | X | X | X | X |
| Height (D) | 7.3/8.2.5 | X | | | | | | | | | | | |
| Weight (D) | 7.4/8.2.5 | X | X | | X | X | X | X | X | X | X | X | X |
| Full neurologic and cardiac assessment for fedratinib pretreated patients (S) | 7.3/8.2.6 | X | | | | | | | | | | | |
| Measurement of spleen by palpation (D) (See Section 8.3.1.1) | 7.4 | X | X | | X | X | X | X | X | X | X | X | X |
| ECOG performance status (D) | 7.4 | X | X | | X | X | X | X | X | X | X | X | |
| 12-lead ECG (D) (See Section 7) | 7.4 | X | X | | X | | X | | | X | | | |
| Adverse events (D) | 7.4/8.2.1 | X | X | X | X | X | X | X | X | X | X | X | X |
| Quality of Life | 7.4/8.3.2 | | | | | | | | | | | | |
| FACT-Lym version 4 (D) | 7.4/8.3.2 | | X | | X | | X | X | | X | | | |
| FACIT-Fatigue Subscale (D) | 7.4/8.3.2 | | X | | X | | X | X | | X | | | |
| Medical resource utilization (D) | 3.3.4/7.4 | | X | | X | X | X | X | X | X | | | |
| Dispense Investigational Product (D) | 7.4 | | | X | X | X | X | X | X | X | X | | |
| Drug Accountability Assessment (D) | 6.5.4/7.4 | | | | X | X | X | X | X | X | X | X | |
| Assess Investigational Product Compliance (D) | 7.4/11.4 | | | | X | X | X | X | X | X | X | | |
| INC424 Dose Administration | 6.1/7.4 | | | X | X | X | X | X | X | X | X | X | |

[redacted]

| Evaluation | Reference to Section | Screening | Baseline | Day 1 | Week 4# | Week 8# | Week 12# | Week 24# | Week 36 | Week 48 | Week 60 & q12w onwards | End of Study/End of Treatment Section 7.6.2 | Follow-up / Study Completion Evaluation Section 7.6.3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit name** | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | | | |
| **Day of visit** | | **-28 to -1** | **-7 to -1** | **Day 1** | **Day 28** | **Day 56** | **Day 84** | **Day 168** | **Day 252** | **Day 336** | | | |
| Record (D) | | | | | | | | | | | | | |
| Survival (D) | 7.6.3.1 | | | | | | | | | | | | X |
| Leukemia-free survival (D) | 11.6.1.1 | | | | | | | | | | | | X |
| Bone marrow biopsy (optional) including percentage blasts (D) | 7.3/8.3.1.2 | | | | | | | | | | | | X |

[redacted]

**Table 7-2 Laboratory assessment schedule**

| Evaluation | Screening | Baseline | Day 1 | Week 4 | Week 8 | Week 12 | Week 24 | Week 36 | Week 48 | Week 60 & q12 wk onwards<br><br>See Section 7.5.1.15 | End of Study/ End of Treatment<br><br>See Section 7.6.2 | Follow-up / Study Completion Evaluation<br><br>See Section 7.6.3 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit number** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | | | |
| **Day of visit** | **-28 to -1** | **-7 to -1** | **Day 1** | **Day 28** | **Day 56** | **Day 84** | **Day 168** | **Day 252** | **Day 336** | | | |
| Hematology (See Appendix III; Section 8.2.8) (D) Reticulocyte count (absolute, %) are optional | X | X | | X | X | X | X | X | X | X | X | X |
| Serum Chemistry (See Appendix III; Section 8.2.8) (D) | X | X | | X | X | X | X | X | X | X | X | X |
| Coagulation (PT, PTT,or INR) See Appendix III; Section 8.2.8. (D) Required for Screening / Baseline, optional after enrollment | X | X | | X | X | X | X | X | X | X | | X |
| Pregnancy Test (for women of childbearing potential). See Section 7.3 and Section 8.2.9.1. (D) | X | | | | | | | | | | | |
| Human immunodeficiency virus antibody test Section 7.3 (S) | X | | | | | | | | | | | |
| Hepatitis A, B, and C (S) (See Section 7.3 and Appendix III ) | X | | | | | | | | | | | |
| Thiamine level testing for fedratinib pretreated patients. Section 7.3 (S) | X | | | | | | | | | | | |

[redacted]

## 7.2 Study evaluations

### 7.2.1 Efficacy

Documentation of disease status will be performed at Screening/Baseline and assessment of spleen response will be repeated at week 4, week 8, week 12, and then every 3 months thereafter, until early discontinuation of the study drug (disease progression; unacceptable toxicity; discontinuation from the study for any other reason; withdrawal of consent; until 24-months after LPFV; or until the drug becomes commercially available in each participating country or, whichever occurs first). Documentation of the Investigator's Assessment of Best Overall Response will be captured. Efficacy will be assessed as outlined in Section 3.3.2.

### 7.2.2 Safety and tolerability

Safety will be monitored by collection of laboratory values (hematology, serum chemistry, coagulation parameters), and patient clinical signs and symptoms as well as collecting of the adverse events at every visit. For details on AE collection and reporting, refer to Section 8.2 and Section 9.

## 7.3 Screening

Prospective participants will be scheduled for a screening visit by study site staff. The required procedures will be scheduled over a -28- to -1-day period. The following procedures will be performed:

- Obtain informed consent before any study specific procedures are conducted.
- Determine if patient meets the inclusion/exclusion criteria (Section 5.2 and Section 5.3).
- A repeat bone marrow biopsy is not required if the diagnostic bone marrow biopsy result is available documenting disease status
- Discussion of methods known to be at least 99% effective in preventing pregnancy (Appendix II). Patients must agree to take appropriate precautions to avoid fathering a child or becoming pregnant while on the study. Additionally, because the effects on male fertility have not been determined, males should not father children for at least 6 months after completing therapy with INC424. Male patients should be informed that if they plan to father children in the future, they may wish to seek counseling on the option of sperm cryopreservation prior to starting study medication.
- Review of medical history and prior medication history (see Section 6.3.1, Permitted Concomitant Therapy). Record the identity and dose of all medications used to treat underlying PMF, PPV MF, or PET-MF. These therapies should not be added, discontinued, or dose-adjusted during the Screening period; patients should continue this stable regimen through the first day of INC424 treatment (Day 1), where applicable.
- Document the risk group of the patient (low, intermediate-1, intermediate-2, high risk).
- Review of transfusion history.
- Comprehensive (complete) physical examination including height, body weight and spleen length. See Section 8.2.3.

[redacted]

- The edge of the spleen shall be determined by palpation, measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion. The spleen should be measured in the same manner at all subsequent visits.
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- ECOG status must be 0, 1, or 2 (Appendix IV).
- 12-lead electrocardiogram (ECG) performed in the recumbent position after 5 minutes of rest.
- Blood sampling for the following (Appendix III):
  - Serum chemistry tests, hematology, coagulation (PT, PTT,or INR). Serum pregnancy test (females of childbearing potential only).
  - Serology tests for HIV.
  - Hepatitis A, B, and C. Hepatitis A (IgM antibody); Hepatitis B (Hepatitis B surface antigen [HBsAg], Hepatitis surface antibody [HBsAb], Hepatitis B IgM core antibody [HBcAb-IgM]); and Hepatitis C (Hepatitis C antibodies [HC Ab], or local health authority requirements.
  - Thiamine level testing for fedratinib pretreated patients as per guidance below.
- For fedratinib pretreated patients there is a need to perform a complete neurologic examination and cardiology assessments to identify any signs or symptoms of thiamine deficiency or Wernicke's Encephalopathy. Thiamine level testing must be documented. MRI of the brain if clinically indicated based on signs and symptoms must be documented as well.
  - In case the patient has any positive signs or symptoms in the neurologic and cardiology assessments before starting ruxolitinib treatment, please ensure a complete description of these in the medical chart.
  - For thiamine level testing, please also ensure that the value is documented in the medical chart.
    - In case of an existing normal thiamine level done in the context of the fedratinib trial follow up there is no need to repeat the test unless clinically indicated based on signs and symptoms.
    - In case of an existing abnormal thiamine level done more than 7 days prior to baseline in the context of the fedratinib trial follow up there is a need to repeat the test and document the value in the medical chart prior to start ruxolitinib treatment. Management of thiamine deficiency should be done as per local usual clinical practice.
    - Patients should have completed or should being receiving thiamine supplementation as per previous investigator's instructions.
  - For MRI of the brain, please also ensure that a complete report is documented in the medical chart.
    - In case of an existing normal MRI done in the context of the fedratinib trial follow up there is no need to repeat the procedure unless clinically indicated based on signs and symptoms.

[redacted]

In case of existing MRI done more than 7 days prior to baseline in the context of the fedratinib trial follow up showing lesions in the brain there is a need to repeat the procedure and document the description of the actual status of those lesions in the medical chart prior to start ruxolitinib treatment. The management of any findings should be done as per usual clinical practice. All inclusion/exclusion criteria (Section 5.2 and 5.3) are to be fulfilled and documented before proceeding to patient enrollment.

An eligibility checklist (Appendix X) has to be completed once all screening procedures are completed. The eligibility checklist will be sent from the site to the Sponsor either by fax or email for evaluation. Upon confirmation of eligibility, the Sponsor will return the signed eligibility checklist to the site by fax or email. The investigator site will then be allowed to enroll patient.

### 7.3.1 Information to be collected on screening failures

**Patients who sign an informed consent but fail to be started on treatment for any reason will be considered a screen failure.** The reason for not being started on INC424 will be entered on the Screening Log eCRFs and includes one of the following reasons: unacceptable or past medical history/concomitant diagnosis; intercurrent medical event; unacceptable laboratory value(s); unacceptable test procedure result(s); did not meet diagnostic/severity criteria; unacceptable use or excluded medication(s)/therapies; subject withdrew consent; unknown; other. In addition, Demography data, Informed Consent information and Inclusion/Exclusion eCRFs must be collected.

No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a SAE during the Screening Phase (see Section 9 for SAE reporting details).

## 7.4 Baseline evaluations (Day -7 to Day -1)

The results from the Screening visit evaluations will be reviewed to determine if the patient continues to meet the eligibility requirements as specified in the protocol. Patients who have signed the informed consent form and meet all the entry criteria (see Inclusion/Exclusion Criteria Section 5.2 and Section 5.3) will be enrolled in the study. Procedures for the Baseline visit may be conducted over 1 to 7 days as needed. Blood samples for hematology and serum chemistry should be performed at least 4 days prior to the intended Study Day 1, in order to allow ample time for results to be returned before administration of INC424. All evaluations should be recorded in the source documents and promptly entered in the eCRF.

The following procedures will be performed at the Baseline visit and prior to enrollment for all patients:

- Confirm that the patient continues to meet all relevant inclusion and exclusion criteria, considering evaluations occurring at screening and baseline.
- Update medication history; confirm all drugs used to treat underlying PMF, PPV MF, or PET-MF.
- Record any concomitant medications.
- Update transfusion history status.

[redacted]

- Blood sampling for serum chemistry tests, hematology, and coagulation (PT, PTT, or INR) (see Appendix III).ECOG status must be 0, 1, or 2 (Appendix IV).
- FACT-Lym version 4 (Appendix VII) and FACIT-Fatigue Subscale (Appendix VIII).
- Medical resource utilization:
  - Number and duration of hospitalization in the past 3 month
  - Number of emergency room visits in the past 3 months
  - Number of general practitioner, specialist, urgent care visits in the past 3 months.
  - Number of transfusions in the past 3 months and baseline transfusion dependency status
  - Number of splenic irradiation treatments in the past 3 months.
- Targeted physical examination including body weight and measurement of spleen by palpation (Section 8.2.3).
- Record adverse events.
- Vital signs (blood pressure, heart rate, 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 min of rest, ONLY if not conducted during the Screening Visit, or if conducted and found to include an abnormality deemed clinically significant.
- Patients will be instructed to discontinue all drugs to treat PMF, PPV MF, or PET-MF on the morning of the Day 1 Visit.

### 7.4.1 Combining Screening and Baseline Visits into 1 Visit

It is permissible to combine the Screening and Baseline visits if necessary, provided all results are available prior to the first dose of INC424

If Screening visit and Baseline visits overlap (-7 to -1)

a. Enter information as required
b. Information requested at both Screening visit and Baseline visit should be entered only once in Screening visit pages

## 7.5 On treatment evaluations

On-treatment evaluations are scheduled for Study Visits at Day 1, and at the end of Weeks 4, 8, 12, and every 12 weeks thereafter. If it is determined at any Study Visit that the patient will discontinue study drug that day, then that study visit will be the End of Study Visit, and the End of Study Visit procedures will be followed.

After 4 weeks of treatment (Week 4 Visit), patients may have the dose of INC424 increased because of inadequate responses. At this visit or anytime during the study, the dose may be adjusted for safety, following the guidelines described in Section 6.2, Dose Modifications. The individual study visit descriptions describe activities that must occur to support and document these dose changes.

This study schedule is designed to closely monitor any drug related adverse events associated with INC424. If, at any time during the study, a patient experiences unexpected signs or

[redacted]

symptoms, additional safety evaluations should be conducted at a regular Study Visit or unscheduled visit. For example, weekly monitoring is advised for patients with platelet counts < 100,000/μL or neutrophils < 1000/μL, and at least twice -weekly for platelets < 50,000/μL or neutrophils < 500/μL. Additionally, x-ray examination of the thorax, echocardiography, and pulmonary function testing and/or arterial blood gas analysis should be considered in patients developing new or worsening cardiopulmonary symptoms including cough, shortness of breath, exercise intolerance or peripheral edema.

Women of childbearing potential will be assessed for pregnancy status, either by serum or urine pregnancy tests, prior to starting treatment with INC424 only (see Section 5.2). If local requirements mandate more frequent testing, applicable sites will conduct monthly testing.

See Section 6.2.2 and Section 6.2.6 for criteria for mandatory reduction, interruption, or discontinuation of study drug based upon results of safety monitoring.

### 7.5.1 On treatment evaluation requirements

#### 7.5.1.1 Day 1

The Day 1 visit may occur as soon all Baseline evaluations have been completed, and the laboratory data (including platelet count) from the Baseline Visit are available. The following procedures will be performed and all observations will be recorded in the eCRF:

- Record any concomitant medications.
- Determine the date and time of last administration of prior therapy (if any) for treatment of PMF, PPV MF, or PET-MF.
- Update transfusion history status.
- Administer the morning dose of INC424, and monitor the patient for adverse events/tolerability.
- Dispense study drug for the first 28 days (plus overage) along with dosing instructions.
  - The importance of compliance will be reviewed with the patient.
  - The patient will be educated on medications and food that should be avoided while taking INC424.
  - The patient and/or family members are to be instructed to telephone the study site with any changes in mental or physical status or questions about INC424, and also to return all unused INC424.
- Patients will be instructed to call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms. These adverse events will be recorded on the eCRF.

#### 7.5.1.2 Week 1 through Week 4

Patients will self-administer INC424 BID as instructed, morning and evening (at approximately 12-hour intervals), in an outpatient setting. Patients will call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms.

[redacted]

Patient may attend the study clinic up to 3 days prior to week 4 to provide blood samples for serum chemistry tests and hematology (Appendix III). The laboratory results should be available for interpretation and potential dose modification on the Week 4 Study Visit.

#### 7.5.1.3 Week 4 (± 7 days)

The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Update transfusion history status.
- Blood sampling for serum chemistry tests, hematology, and optional coagulation (PT, PTT, or INR) (see Appendix III).
- A targeted physical examination will be performed, including body weight and measurement of spleen by palpation (Section 8.2.3).
- provided **all** requirements for dose at week 4 according to starting INC424 dose as follows:
  - By 5 mg BID if palpable spleen length reduced by less than 40% relative to Baseline, provided **all** requirements for dose increase are met (see Section 6.2.1.1).
  - The dose increase may only be an increase of 5 mg o.d. (e.g., for those patients starting INC 424 at 5 mg PO BID to 5 mg QAM and 10 mg QPM).
- All changes in dose, including rationale for dose increase, should be recorded in the eCRF.
- The dose of INC424 may need to be decreased or interrupted because of low platelet counts or ANC levels (see Section 6.2.2).
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Determination of ECOG performance status (see Appendix IV).
- Complete FACT-Lym version 4 (Appendix VII).and FACIT-Fatigue Subscale (prior to examination) (Appendix VIII).
- Medical Resource Utilization in the past month:
  - Number and duration of each hospitalization.
  - Number of emergency room visits.
  - Number of urgent care visits.
  - Number of additional general practitioner and specialist office visits.
  - Number of transfusions and transfusion dependency status.
  - Splenectomy or splenic irradiation.
- 12-lead ECG performed in the recumbent position after 5 minutes of rest.
- Drug accountability assessment (see Section 6.5.4).
- Assessment of patient compliance.
- Record adverse events.
- Study drug for the next 28 days (plus overage) will be dispensed along with dosing instructions.
- Patients will be instructed to call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms.

[redacted]

#### 7.5.1.4 Week 4 through Week 8

Patients will self-administer INC424 BID as instructed, morning and evening in an outpatient setting. Patients will call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms.

#### 7.5.1.5 Week 8 (± 7 days)

The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Update transfusion history status.
- A targeted physical examination will be performed, including body weight and measurement of spleen by palpation (Section 8.2.3).
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Blood sampling for serum chemistry tests, hematology, and optional coagulation (PT, PTT, or INR) (see Appendix III).
- Determination of ECOG performance status (see Appendix IV).
- MRU in the past month:
  - Number and duration of each hospitalization.
  - Number of emergency room visits.
  - Number of urgent care visits.
  - Number of additional general practitioner and specialist office visits.
  - Number of transfusions and transfusion dependency status.
  - Splenectomy or splenic irradiation.
- Document new (changed) or ongoing dose information for INC424. Dose changes that are necessary between study visits will be communicated immediately and directly to the patient by telephone; the communication will be documented in the source documents.
- Drug accountability assessment (see Section 6.5.4).
- Assess patient compliance.
- Record adverse events.
- Study drug for the next 28 days (plus overage) will be dispensed along with dosing instructions.
- Patients will be instructed to call the investigator or designated research staff if they experience any signs and/or symptoms. These adverse events will be recorded on the eCRF. Patients will be reminded to bring the study drug to the clinic with them.

#### 7.5.1.6 Week 8 through Week 12

Patients will self-administer INC424 BID as instructed, morning and evening in an outpatient setting. Patients will call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms.

[redacted]

#### 7.5.1.7 Week 12 (± 7 days)

The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Update transfusion history status.
- A targeted physical examination will be performed, including body weight and measurement of spleen by palpation (Section 8.2.3).
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Blood sampling for serum chemistry tests, hematology, and optional coagulation (PT, PTT, or INR) (see Appendix III).
- 12-lead ECG performed in the recumbent position after 5 minutes of rest.
- Determination of ECOG performance status (see Appendix IV).
- Complete FACT-Lym version 4 (Appendix VII) and FACIT-Fatigue Subscale (prior to examination) (Appendix VIII)
- MRU in the past month:
  - Number and duration of each hospitalization.
  - Number of emergency room visits.
  - Number of urgent care visits.
  - Number of additional general practitioner and specialist office visits.
  - Number of transfusions and transfusion dependency status.
  - Splenectomy or splenic irradiation.
- Document new (changed) or ongoing dose information for INC424. Dose changes that are necessary between study visits will be communicated immediately and directly to the patient by telephone; the communication will be documented in the source documents.
- Drug accountability assessment (see Section 6.5.4).
- Assess patient compliance
- Record adverse events.
- Study drug for the next 84 days (plus overage) will be dispensed along with dosing instructions.
- Patients will be instructed to call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms. These adverse events will be recorded on the eCRF. Patients will be reminded to bring the study drug to the clinic with them.

#### 7.5.1.8 Week 12 through Week 24

Patients will self-administer INC424 twice daily as instructed, morning and evening, in an outpatient setting. Patients will call the Investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms.

Those patients who underwent dose modifications at the Week 12 (Month 3) visit must return to the clinic as follows:

[redacted]

- Patients experiencing hematologic adverse events - following laboratory draws as outlined in Section 6.2.2.
- Patients who underwent dose escalation at week 12 (Month 3) should return to the clinic for serum chemistries and hematology assessments.

#### 7.5.1.9 Week 24 (± 7 days)

The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Update transfusion history status.
- A complete physical examination will be performed, including body weight and measurement of spleen by palpation (Section 8.2.3).
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Blood sampling for serum chemistry tests, hematology, and optional coagulation (PT, PTT, or INR) (see Appendix III).
- Determination of ECOG performance status (see Appendix IV).
- Complete FACT-Lym version (Appendix VII) and FACIT-Fatigue Subscale (prior to examination) (Appendix VIII).
- Medical resource utilization in the past month:
  - Number and duration of each hospitalization.
  - Number of emergency room visits.
  - Number of urgent care visits.
  - Number of additional general practitioner and specialist office visits.
  - Number of transfusions and transfusion dependency status.
  - Splenectomy or splenic irradiation.
- Drug accountability assessment (see Section 6.5.4).
- Record adverse events.
- Assess patient compliance.
- Document new (changed) OR ongoing dose information for INC424. Dose changes that are necessary between study visits will be communicated immediately and directly to the patient by telephone; the communication will be documented in the source documents.
- INC424 for the next 84 days (plus overage) will be dispensed along with dosing instructions.
- Patients will be instructed to call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms. Patients will be reminded to bring the study drug to the clinic with them.

#### 7.5.1.10 Week 24 through Week 36

Patients will self-administer INC424 BID as instructed, morning and evening in an outpatient setting. Patients will call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms.

[redacted]

#### 7.5.1.11 Week 36 (± 7 days)

The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Update transfusion history status.
- A complete physical examination will be performed, including body weight and measurement of spleen by palpation (Section 8.2.3).
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Blood sampling for serum chemistry tests, hematology, and optional coagulation (PT, PTT, or INR) (see Appendix III).
- Determination of ECOG performance status (see Appendix IV).
- MRU in the past month:
  - Number and duration of each hospitalization.
  - Number of emergency room visits.
  - Number of urgent care visits.
  - Number of additional general practitioner and specialist office visits.
  - Number of transfusions and transfusion dependency status.
  - Splenectomy or splenic irradiation.
- Drug accountability assessment (see Section 6.5.4).
- Record adverse events.
- Assess patient compliance.
- Document new (changed) OR ongoing dose information for INC424. Dose changes that are necessary between study visits will be communicated immediately and directly to the patient by telephone; the communication will be documented in the source documents.
- INC424 for the next 84 days (plus overage) will be dispensed along with dosing instructions.
- Patients will be instructed to call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms. Patients will be reminded to bring the study drug to the clinic with them.

#### 7.5.1.12 Week 36 through Week 48

Patients will self-administer INC424 BID as instructed, morning and evening, in an outpatient setting. Patients will call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms.

#### 7.5.1.13 Week 48 (± 7 days)

The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Update transfusion history status.

[redacted]

- A complete physical examination will be performed, including body weight and measurement of spleen by palpation (Section 8.2.3).
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Blood sampling for serum chemistry tests, hematology, and optional coagulation (PT, PTT, or INR) (see Appendix III).
- 12-lead ECG performed in the recumbent position after 5 minutes of rest.
- Determination of ECOG performance status (see Appendix IV).
- Complete FACT-Lym version 4 (Appendix VII) and FACIT-Fatigue Subscale (prior to examination) (Appendix VIII).
- Medical resource utilization in the past month:
  - Number and duration of each hospitalization.
  - Number of emergency room visits.
  - Number of urgent care visits.
  - Number of additional general practitioner and specialist office visits.
  - Number of transfusions and transfusion dependency status.
  - Splenectomy or splenic irradiation.
- Drug accountability assessment (see Section 6.5.4).
- Assess patient compliance.
- Record adverse events.
- Document new (changed) *OR* ongoing dose information for INC424. Dose changes that are necessary between study visits will be communicated immediately and directly to the patient by telephone; the communication will be documented in the source documents.
- INC424 for the next 84 days (plus overage) will be dispensed along with dosing instructions.
- Patients will be instructed to call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms. Patients will be reminded to bring the study drug to the clinic with them.

#### 7.5.1.14 Weeks 49 and afterwards

Patients will self-administer INC424 BID as instructed, morning and evening (at approximately 12-hour intervals), in an outpatient setting. Patients will call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms.

#### 7.5.1.15 Weeks 60 (± 7 days) and each 12 Weeks thereafter (Week 72, 84, 96, etc)

The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Update transfusion history status.

[redacted]

- A targeted physical examination will be performed, including body weight and measurement of spleen by palpation (Section 8.2.3).
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Blood sampling for serum chemistry tests, hematology, and optional coagulation (PT, PTT, or INR) (see Appendix III).
- Determination of ECOG performance status (see Appendix IV).
- Record adverse events.
- Document new (changed) OR ongoing dose information for INC424. Dose changes that are necessary between study visits will be communicated immediately and directly to the patient by telephone; the communication will be documented in the source documents.
- INC424 for the next 84 days (plus overage) will be dispensed along with dosing instructions.
- Drug accountability assessment (see Section 6.5.4)
- Assess patient compliance.
- Patients will be instructed to call the investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms. Patients will be reminded to bring the study drug to the clinic with them.

#### 7.5.1.16 Missed/moved visit

If a visit is moved or missed, the next scheduled visit should comply as much as possible with the original schedule.

## 7.6 End of treatment visit, including premature withdrawal and study discontinuation visit

Patients who discontinue study treatment before the end of the study should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the End of Treatment (EOT) visit will be performed. The appropriate eCRF page should be completed, giving the date and reason for stopping the study treatment. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 28 days following the last dose of study treatment.

### 7.6.1 Criteria for premature withdrawal

Patients may voluntarily withdraw from the study at any time without penalty of jeopardizing their health care or loss of benefits to which the patient is otherwise entitled or be dropped from it at the discretion of the investigator at any time. Every reasonable effort should be made to determine the reason a patient withdraws prematurely and this information should be recorded in the eCRF. A patient may be withdrawn from the study if, in the investigator's medical judgment, the patient is non-compliant with the study requirements. A patient MUST be withdrawn from the study if she becomes pregnant, or if he intends to father a child during the anticipated duration of study participation. The investigator MUST discontinue a patient from the study if the following occurs:

[redacted]

- Consent is withdrawn.
- Further participation would be injurious to the patient's health or well-being in the investigator's medical judgment.
- The study is terminated.
- If the study drug has been interrupted for 8 weeks or more for any reason, except in the case of splenectomy where a maximum of 12 weeks of drug interruption is permitted.
- The study drug has been permanently discontinued for safety according to the criteria specified in Section 6.2.6. Specifically:
- **Hematologic toxicity**. The lowest allowed dose (5 mg BID or 5 mg QD with concomitant CYP3A4 inhibitor or those patients with low platelet counts [50,000 – <100,000/μL ]) is not tolerated due to the following:
  - Platelets cannot be maintained ≥50,000/μL.
  - Absolute neutrophil count cannot be maintained ≥500/μL.
  - Hemoglobin cannot be maintained ≥6.5g/dL despite the use of transfusion therapy (or if the patient will not accept blood transfusions).
- **Non-hematologic toxicity**. The lowest allowed dose (5 mg BID or 5 mg QD with concomitant CYP3A4 inhibitor or those patients with low platelet counts [50,000 – <100,000/μL ]) is not tolerated due to the following:
  - The occurrence of a Grade 4 laboratory abnormality that is considered at least possibly related to the study drug, and is clinically significant in the view of the investigator. Exceptions NOT requiring study withdrawal are serum iron, total bilirubin not accompanied by direct bilirubin of 2 x ULN, triglycerides, total cholesterol, HDL cholesterol, not accompanied by at least a Grade 3 elevation of serum creatinine.
  - Recurrence of a Grade 4 clinical event (non-laboratory based) after re-challenge with the study drug. Exceptions NOT requiring study withdrawal are fatigue, insomnia, obesity, constitutional symptoms (disabling but not life threatening), salivary gland changes, arthritis, and joint effusion.

Study drug MAY be permanently discontinued for a Grade 4 clinical event that has NOT been confirmed upon rechallenge with the study drug, at the option of the investigator.

### If a patient is withdrawn from the study:

- The study Medical Monitors (Sponsor and CRO) must be notified.
- The reasons for discontinuation must be documented in the patient's medical record and eCRF.
- The End of Treatment Visit procedures should be completed at the last study visit while patient is receiving INC424 study drug.
- The Follow-up Visit should be performed 28 to 37 days after the last dose of study drug was taken (i.e., 28 - 37 days after the End of Study Visit).

[redacted]

### 7.6.2 End of treatment evaluations

#### 7.6.2.1 End of study or early termination visit

The End of Study or Early Termination Visit constitutes the final study visit where study drug has been taken. An End of Study Visit may occur with a planned discontinuation for any reason (e.g., at Week 20, it is determined that patient will participate in the study only 1 more month; therefore, the Week 24 Visit will become the End of Study Visit).

The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Update transfusion history status.
- A targeted physical examination will be performed, including body weight and measurement of spleen by palpation (Section 8.2.3).
- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Blood sampling for serum chemistry tests, hematology (see Appendix III).
- Determination of ECOG performance status (see Appendix IV).
- Drug accountability assessment (see Section 6.5.4).
- Record adverse events.
- Document the dose the patient was on at the time of study discontinuation.
- Patients will be asked to return to the clinic between 28 and 37 days later for a final Follow-up Visit.
- The sponsor (Novartis Pharmaceuticals) will be notified of the patient withdrawal.

### 7.6.3 Follow-up period

All patients must have safety evaluations for 28 days after the last dose of study treatment.

Patients lost to follow up should be recorded as such on the eCRF. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

#### 7.6.3.1 Follow-up evaluations

The following evaluations will be performed 28 to 37 days after the completion of the End of Study or Early Termination Visit or approximately 1 month post-dosing for a patient who is discontinuing from the study:

The following procedures will be performed and all observations will be recorded in the eCRF:

- Review of concomitant medications.
- Review of transfusion history.
- A complete physical examination will be performed, including body weight and measurement of spleen by palpation.

[redacted]

- Vital signs (blood pressure, heart rate, respiratory rate and body temperature) to be performed in a sitting position after 5 minutes of rest.
- Blood sampling for serum chemistry tests, hematology, and optional coagulation (PT, PTT, or INR) (see Appendix III).
- Record adverse events.
- Survival assessments (Overall, LFS, PFS).

# 8 Study assessments

## 8.1 Demographic and other pretreatment assessments

After written informed consent is obtained, demographic data and a complete medical and medication history will be collected at Screening. Height and body weight measurements will be done and body mass index will be calculated in the database

## 8.2 Safety assessments

### 8.2.1 Adverse events

AEs will be monitored continuously during the study. Patients will be instructed to report all AEs during the study and patients will be assessed for the occurrence of AEs throughout the study. In order to avoid bias in eliciting AEs, patients will be asked general, non-leading questions such as "How are you feeling?" All AEs (serious and non-serious) must be recorded on the source documents and case report forms regardless of the assumption of a causal relationship with the study drug. The definition, reporting, and recording requirements for AEs are described in Section 9.

#### 8.2.1.1 Assessment of causality

Every effort should be made by the investigator to explain each adverse event and assess its relationship, if any, to study drug treatment. Causality should be assessed using the following categories: no (not related), or yes (reasonable possibility).

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of the following:

1. Known pharmacology of the drug
2. Reaction of a similar nature being previously observed with this drug or class of drug.
3. The event having often been reported in the literature for similar drugs as drug related (e.g. skin rashes, blood dyscrasias).
4. The event being related by time to drug administration terminating with drug withdrawal (dechallenge) or reproduced on rechallenge.

The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE form. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

[redacted]

### 8.2.2 Safety assessments at investigational therapy withdrawal

All the safety assessments performed at the every 4 or 12-week visit should be performed at the time of investigational therapy conclusion or withdrawal.

### 8.2.3 Physical examinations

A comprehensive physical examination will be performed as noted in the Description of Study Visits (Table 7-1 and Table 7-2). The comprehensive physical examination will include the following organ/body system assessments: general appearance, skin; HEENT (head, eyes, ears, nose and throat); thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; neurological examination, assessment of edema and extremities. A targeted physical examination will be performed as indicated in Section 7.5 (On-Treatment Evaluations) and will always include liver and spleen, and assessment of edema. In addition, the targeted physical examination will include body systems as indicated by patient symptoms, AEs, prior physical examinations, or other findings as determined by the investigator. Both complete and targeted physicals will include a measurement of spleen length, assessed by palpation, and measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion.

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

### 8.2.4 Vital signs

Vital sign measurements including blood pressure, heart rate, respiratory rate, and body temperature will be collected on the days noted in the Description of Study Visits (Section 7.1). After the patient has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, e.g. OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

### 8.2.5 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

### 8.2.6 Full neurologic examination and cardiology assessments

For fedratinib pretreated patients there is a need to perform neurologic and cardiology examinations to identify any sign of thiamine deficiency or Wernicke's Encephalopathy which common symptoms or signs at disease presentation are: ocular abnormalities, mental status changes, and incoordination of gait and trunk ataxia. Uncommon symptoms or signs at presentation have to be also assessed: stupor, hypotension and tachycardia, hypothermia,

[redacted]

bilateral visual disturbances and papilledema, epileptic seizures, hearing loss, hallucinations and behavioral disturbances.

### 8.2.7 12-lead ECG

Twelve-lead ECGs will be obtained for each patient during the study as per the Description of Study Visits (Table 7-1). Baseline ECGs will be obtained at Screening. All 12-lead ECGs obtained at subsequent time points during the study will be compared with this pre-study treatment 12-lead ECG as follows:

- For ECG morphology, all post-dose ECG recordings will be compared to the Screening/Baseline ECG tracing.
- For the calculation of changes in cardiac intervals (QT interval), the intervals from the Screening will be used as the Baseline for comparison of all post dose intervals.

Interpretation of the tracing must be made by a qualified physician and documented on the ECG eCRF page. Each ECG tracing should be labeled with the study number, patient initials (where regulations permit), patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities present when the patient signed informed consent should be reported on the Medical History eCRF page. Clinically significant findings must be discussed with the Novartis Medical Monitor prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page.

### 8.2.8 ECG analysis and reporting

The investigator or another appropriately trained individual will perform the initial ECG analysis of the data collected for each patient. All ECGs will be analyzed according to ECG abnormality criteria defined in cooperation with the Sponsor and taking into account the protocol requirements.

### 8.2.9 Clinical safety laboratory assessments

Clinical laboratory tests [hematology, serum chemistry, and coagulation (PT, PTT, or INR)] will be performed at the center where the patient is enrolled. All patients will have samples of blood collected on the days noted in the Description of Study Visits (Table 7-2) for analysis of serum chemistry, hematology, and coagulation (PT, PTT, or INR). Coagulation tests are required for screening and or baseline, and are optional after enrollment. Appendix III provides a complete list of blood chemistry and hematology tests that will be performed.

Hemoglobin, hematocrit, WBC count with differential (neutrophils. lymphocytes, eosinophils, basophils, monocytes, and blast cells) and platelet count will be measured. RBC sediment rate (where available) will also be measured.

Recticulocyte count (absolute and % reticulocytes) is optional.

Serum creatinine, total or direct bilirubin, AST, ALT, alkaline phosphatase (where available).

Thiamine blood level testing for fedratinib pretreated patients as per guidance described in Section 7.3.

[redacted]

#### 8.2.9.1 Pregnancy test

Patients who are older than age 55 and have a history of amenorrhea for 1 year, or patients who have been surgically sterile for at least 3 months, will not be considered to be of childbearing potential. All other female patients will have pregnancy test within 14 days prior to Day 1 of INC424.

A positive urine pregnancy test requires immediate interruption of study treatment until serum B-hCG is performed and found to be negative. If positive, the patient must be discontinued from the study.

#### 8.2.9.2 Serology

A complete list of serology tests to be performed at the Screening Visit is provided in Appendix III.

## 8.3 Symptom and functional response assessments

### 8.3.1 Response assessments

#### 8.3.1.1 Primary response assessments

**Spleen length:** Spleen length will be assessed by manual palpation at every study visit, and will be used to determine if dose increases for lack of efficacy should be considered. investigators will be provided with a soft centimeter ruler so that palpable spleen length is measured in centimeters and not in finger breadths. The edge of the spleen shall be determined by palpation, and measured in centimeters, using a soft ruler, from the costal margin to the point of greatest splenic protrusion.

#### 8.3.1.2 Additional response assessments

A bone marrow biopsy will be collected only if it is a normal routine of the attending physician, and is not mandatory.

### 8.3.2 Quality of Life assessments

Patients with MPNs often present with significant constitutional symptoms that interfere with their QoL including splenomegaly, pruritus, weight loss, weakness, night sweats. The effect of INC424 on patient QoL will be measured using several assessment tools including ECOG performance status (See Appendix IV) and the FACT-Lym version 4 (See Appendix VII) and FACIT-Fatigue Subscale tools (See Appendix VIII).

#### 8.3.2.1 FACT-Lym Scale (version 4)

The FACT measurement system is a collection of self-report scales of health reported quality of life (HRQOL) for people with cancer (Cella 1993) See Appendix VII.

#### 8.3.2.2 FACIT-Fatigue Scale

The FACIT Fatigue (FACIT-F) questionnaire was developed to assess fatigue associated with anemia and includes 13 fatigue-related questions (FACIT fatigue). The responses to the 13

[redacted]

items in the questionnaire are each measured on a 4-point Likert scale (Cella et al 1993). Thus, the total score ranges from 0 to 52. High scores represent less fatigue. The FACIT Fatigue Scale has been validated in the general population, in patients with cancer and in patients with RA. In patients with cancer, the FACIT Fatigue Scale showed excellent internal consistency and reliability and differentiated patients by hemoglobin level and patient-related performance status (Chandran 2007).

Cella et al (2002) determined the minimally important difference (MID) of the FACIT-Fatigue scale to be 3 points.

Subjects will complete this assessment at Baseline and at each visit as indicated in Table 7-1.

### 8.3.3 Resource utilization

Medical resource utilization will be captured at each visit out to 48 weeks. Data collection will include medical resources utilized since the last visit. MRU includes office visits (general practitioner and specialist visits), procedures/treatments, emergency room visits, urgent care visits, hospitalizations, transfusions, splenectomy, splenic radiation and changes in concomitant medications.

[redacted]

# 9 Safety monitoring and reporting

## 9.1 Adverse events

### 9.1.1 Definition and reporting

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

Adverse events that begin or worsen after informed consent should be recorded in the Adverse Events 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 28 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 CTCAE version 3.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected though a Death form.

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

- The severity grade (CTCAE Grade 1-4)
- Its duration (Start and end dates)
- Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
- Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
- Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
- Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequalae, fatal, unknown)

[redacted]

- Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event 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 treatment, the interventions required to treat it, and the outcome.

Progression of myelofibrosis, including leukemic transformation (including fatal outcomes), if documented by use of appropriate method, should not be reported as a serious adverse event.

Adverse events separate from the progression/ transformation of myelofibrosis (example, pneumonia at the time of progression or septic shock concurrent with finding of AML) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

All AEs occurring from the first dose of investigational product until 28 days after the last dose must be recorded regardless of whether or not they are considered drug related.

All subjects who have AEs, whether considered associated with the use of the investigational product or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the AE result in death, a full pathologist's report should be supplied if and when available.

SAEs must be reported as outlined in Section 9.2.2. In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions must also be reported.

#### 9.1.1.1 Events related to disease under study

Worsening of a pre-existing illness other than disease under study will be assessed as an AE.

Worsening of a sign or symptom of the disease under treatment will normally be measured by efficacy parameters and not considered an AE unless the Sponsor or the reporting physician considers that the study drug contributed to the worsening.

#### 9.1.1.2 Surgical procedures related to disease under study

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event, if it occurs or is detected during the study period.

### 9.1.2 Laboratory test abnormalities

#### 9.1.2.1 Definition and reporting

Laboratory abnormalities that constitute an AE in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events eCRF. Whenever possible, a

[redacted]

diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

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

## 9.2 Serious adverse events

### 9.2.1 Definitions

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

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - 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

Progression of myelofibrosis, including leukemic transformation (including fatal outcomes) are exempted from SAE reporting.

This information is collected in the study as part of study endpoints: progression free survival (PFS) and acute myeloid leukemia free survival (LFS).

### 9.2.2 Reporting

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 28 days after the patient has stopped study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after this 28 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study treatment. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original

[redacted]

episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

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

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

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

## 9.3 Pregnancies

Pregnancy, in and of itself, is not regarded as an AE, unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method.

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

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

The procedures that will be followed based on whether a pregnancy is confirmed by a positive serum or urine test result are listed below:

- Investigator and subject must notify each other immediately.
- Investigator must notify the Sponsor immediately.
- Discontinue study drug immediately.
- Perform the required End-of-treatment visit study evaluations.

[redacted]

- Investigator must complete and submit the Pregnancy Initial and Follow-up report forms to the Sponsor.
- A serum pregnancy test must be performed to confirm the urine test result. (The serum test should be performed at the investigative site to ensure the test will be performed promptly and the result available immediately for review.)
- Withdraw the patient from the study.

If a negative serum test does not confirm the urine test result, then:

- The investigator will use his/her expert judgment, based on an assessment of the potential benefit/risk to the subject, to determine if it is in the patients best interest to resume study drug and continue participation in the study.

Any pregnancy diagnosed during the study, or that occurs within 28 days after stopping study drug, must be reported immediately to the investigator. The investigator will notify the Sponsor or designee by following the procedures described in Section 9.2.2. The outcome of all such pregnancies (i.e., spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be documented and followed-up on a form that will be provided by the Sponsor. The pregnancy will be followed to term and the outcome, including any premature termination, must be reported to the Sponsor. All live births must be followed for a minimum of 30 days or to the first well-baby visit. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for this study. Elective abortion procedures, without complications, should not be considered as AEs.

### 9.4 Warning and precautions

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

## 10 Data collection and management

### 10.1 Data confidentiality

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

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

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject

[redacted]

authorization. For subjects 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 subject 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.

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

## 10.2 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative or authorized designee 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 eCRFs, the adherence to the protocol and 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 on eCRFs must be traceable to these source documents in the patient's file. Data not requiring a separate written record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data (see items listed as Category "D" in Table 7-1 and Table 7-2). 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 to confirm their consistency with the eCRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

[redacted]

## 10.3 Data collection

The designated investigator staff will enter the data required by the protocol into the 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 modification or verification of the entered data by the investigator staff before transfer to Novartis (or designated CRO) via a secure network. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

In addition, data collected will include:

- information about previous fedratinib treatment and the end date,
- for those patients with fedratinib treatment:
  - information about ruxolitinib received or not,
  - and if ruxolitinib received, information on receipt when participating to CINC424A2401 or not will be collected. For patient enrolled previously in CINC424A2401, previous patient number will be collected.

## 10.4 Database management and quality control

Data will be entered into the study database by Investigator/Study Coordinator for electronic data capture (EDC) studies.

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Detected discrepancies for which the resolution is obvious/self-evident will be corrected by Novartis Data Management personnel (or designated CRO). Electronic data queries are stating the nature of the problem and requesting clarification will be created for all other discrepancies and missing values and sent to the investigational 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.

At the conclusion of the study the occurrence of any protocol deviations will be determined. After these actions have been completed and 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 Statistical Reporting and the Global Therapeutic Area Head.

[redacted]

# 11 Statistical methods and data analysis

The primary objective of this study is to collect safety data on patients with PMF, PPV MF, or PET-MF treated by INC424, while secondary objectives are on collecting some efficacy data and medical resource use.

This section is describing all analyses to be performed, the primary and secondary objective being descriptive; no hypotheses testing will be performed.

The data will be analyzed by Novartis. All data from all centers that participate in this protocol will be combined and analyzed together.

## Timing of analyses

The primary analysis will be performed after all patients have either completed 24 months of treatment or have been prematurely discontinued from the study. All patients should have been followed for 28 days after they have discontinued INC424, data collected during this follow-up period will be included in the analysis. An interim analysis planned for this study will take place when 50 patients with low platelets will have completed 6 months of treatment.

Additional analyses may also be performed if needed to fulfill regulatory obligation or publication purpose.

## Statistical reporting and grouping

Data will be analyzed according to platelet count at baseline and displayed considering the following two groups:

- Low platelet patients (platelets < 100, 000 /μL)
- and non-low platelets (platelets ≥ 100, 000 /μL).

All analyses for categorical data will be presented as frequencies and percentages (% based on number of patients from the considered population unless specified otherwise).

For all continuous data, except time related ones, the following descriptive statistics will be presented: n, mean, standard deviation, median, minimum and maximum. Time related data (i.e. durations such as overall survival) will be summarized using n, median, minimum and maximum.

For all analyses, **baseline value** will be defined as the latest available assessment obtained prior to the date of first dose of study drug administration. If assessment prior to first dose of study drug administration is not available, then assessment on the day of first dose of study drug administration will be used at baseline.

All data considered in the analysis will be listed individually.

Please note: due to the trial design and intent, it is not possible to ensure that a sufficient number of patients will be available to conduct the analyses as planned. Therefore, it is important to consider that certain analyses described in the subsequent section may not be relevant if study population is too small.

[redacted]

## 11.1 Handling of missing values

No imputation for missing data will be performed, unless otherwise specified

## 11.2 Populations for analysis

**Full Analysis Set (FAS)** consists of all patients who received at least one administration of study drug.

**Safety set** consists of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment.

Please note: the statement that a patient had no adverse events (on the Adverse Event CRF) constitutes a safety assessment. Patients who have received at least one dose of study drug but who have no post-treatment safety data of any kind would be excluded from the safety population.

**Per protocol set**: Consists of all FAS patients without any major protocol deviation. Rules for identifying major protocol deviations will be detailed in RAP.

## 11.3 Patient demographics/other baseline characteristics

Demographic (gender, age, weight, height, BMI) and other baseline data (disease characteristics, medical history, medication history, and serology) will be summarized descriptively for all patients of the FAS.

## 11.4 Treatments (study drug, concomitant therapies, compliance)

All analyses from this section will be performed on all patients from the safety set.

Duration of INC424 administration will be summarized using descriptive statistics. Also, proportion of patients by dose intensity range will be presented.

Frequency of dose reductions and interruptions will be summarized by reason, if available. The duration of the dose interruptions will also be summarized.

Concomitant medications and significant non-drug therapies prior to and after the start of the study drug will be summarized by ATC code.

## 11.5 Primary objective

The primary objective of this study is to collect safety data on patients with PMF, PPV MF, or PET-MF treated by INC424. This will be assessed considering incidence of treatment-emergent AEs.

The safety set will be used for the analysis of clinical safety data.

### 11.5.1 Variables

Primary analysis will be performed on the **incidence of treatment-emergent AEs.**

Incidence of a given AE is defined as the ratio of total number of patients experiencing at least once this AE (defined by its preferred term) divided by the total number of patients in the safety set.

[redacted]

A treatment-emergent AE is an AE that starts during treatment (including the 28 days following last treatment administration) or worsen on treatment.

### 11.5.2 Statistical hypothesis, model, and method of analysis

No hypotheses or models will be considered for these analyses, descriptive statistics will be provided.

The treatment-emergent AEs only will be summarized, while all reported AEs will be included in listing.

In this section the term **adverse event** or AE refers only to treatment-emergent AEs unless specified otherwise.

The incidence of AEs will be tabulated by MedDRA® (Medical Dictionary for Regulatory Activities) preferred term and by system organ class (SOC).

Incidence of AEs will also be summarized by system organ class, severity (based on CTCAE grades).

The same analysis will be repeated for SAEs regardless of drug relationship, drug related SAEs, AEs which CTCAE grade is 3 or 4 and for drug related AEs.

AEs that will not have relationship to study drug specified will be considered to be treatment-related.

## 11.6 Secondary objectives

### 11.6.1 Efficacy

This study provides an opportunity to collect further data on INC424 efficacy, resource use and patient's quality of life in patients with PMF, PPV MF, or PET-MF. For this reason, the following exploratory analysis will be conducted.

#### 11.6.1.1 Full analysis set will be used for all efficacy analyses

The following endpoints are considered in assessing efficacy of INC424 in the study population.

**Best overall response** to treatment as assessed by spleen palpation, is defined by the investigator.

**Change of spleen length from Baseline to end of each visit and at end of treatment**. This parameter is computed by dividing the difference of spleen length at assessment time and at baseline by the length at baseline multiplied by one hundred.

**WBC and platelet count changes from Baseline at end of each visit and at end of treatment**. For each parameter, the percent of change will be computed by dividing the difference of value at assessment time and at baseline by the value at baseline, and multiplying by one hundred.

[redacted]

**Shift in fibrosis in the bone marrow from Baseline**, is defined as the status change of fibrosis at time of worst/best response (whenever it occur) compared to fibrosis status at baseline. Assessment of fibrosis in the bone marrow after enrollment is not mandatory.

**Progression free survival (PFS)** is the time from first study drug administration to date of documented progression (based on International Working Group for Myelofibrosis Research and Treatment Response Criteria, IWG-MRT) (Tefferi A, Barosi G, Mesa RA, et al (2006) or deaths. Time will be censored at the last date the patient is known to be free of disease progression for patients without event.

**Leukemia free survival (LFS)** is the time from the first study drug administration date to: the date of the bone marrow blast count ≥20% OR the date of the first peripheral blood blast count ≥20% that is subsequently confirmed to have been sustained for at least 8 weeks or the date of death, whichever occurs first. LFS will be computed whenever data of bone marrow blast and/or peripheral blood blast counts is/are available. Time will be censored at the last date the patient is known to be free of leukemia for patients without event.

**Overall survival (OS)** is the time from first study drug administration to date of deaths (whatever the cause). Time will be censored at the last date the patient is known to be alive for patients without event.

#### 11.6.1.2 Statistical hypothesis, model, and method of analysis

The proportion of patients by best overall response category will be summarized. Proportion of responders will be estimated and its 95% confidence intervals provided.

Change in spleen length from Baseline to end of each visit/month of therapy and at end of treatment will be described using descriptive statistics and by relevant change categories (*e.g.* (≤50%, (-50%, -25%], (-25%, -5%], (-5%, 5%], (5%, 25%], (25%, 50%] and >50%).

WBC and platelet count changes from baseline will be summarized using descriptive statistics at the end of each visit and at the end of treatment.

Number and proportion of patients by fibrosis status change from Baseline will provided for each possible combination.

PFS, LFS, and OS will be estimated with the Kaplan Meier method and 95% confidence intervals will be provided for the estimated median.

### 11.6.2 Laboratory abnormalities

All laboratory values will be converted into SI units and the severity grade calculated using appropriate common toxicity criteria (CTCAE).

#### 11.6.2.1 Hematology

A listing of laboratory values will be provided by laboratory parameter. A separate listing will display notable laboratory abnormalities (*i.e.* newly occurring CTCAE grade 3 or 4 laboratory toxicities).

The frequency of laboratory abnormalities will be displayed by parameter.

Laboratory data will be summarized by presenting shift tables.

[redacted]

#### 11.6.2.2 Biochemistry

A listing of laboratory values will be provided by laboratory parameter. A separate listing will display notable laboratory abnormalities (*i.e.* newly occurring CTCAE grade 3 or 4 laboratory toxicities).

The frequency of laboratory abnormalities will be displayed by parameter.

Laboratory data will be summarized by presenting shift tables.

### 11.6.3 Other safety data: weight, vital signs, ECG, and death

Weight change from Baseline will be described at each assessment time. Frequency of weight relative change by more than 20% will be summarized. Patients exhibiting clinically notable abnormalities will be listed.

Descriptive statistics and mean change from Baseline will be determined for vital signs (oral temperature, blood pressure and pulse) at each assessment time. Frequency of clinically notable abnormalities will be summarized. Patients exhibiting clinically notable abnormalities will be listed.

Notably abnormal changes in ECG parameters will be displayed in listings.

Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE.

Death rate (any death) at end of study will be summarized, if sufficient number, rate by cause, SOC, and preferred term will also be tabulated, else death and cause will only be listed.

### 11.6.4 Tolerability

#### 11.6.4.1 Resource utilization

Frequency of hospitalization, of emergency room visits, urgent care visits, additional general practitioner and specialist office visits, and splenic irradiation will be summarized at end of each quarter (i.e. every three months after start of study medications).

Overall duration of hospitalization at end of study will be summarized.

The proportion of patients who are transfusion dependent as well as the proportion of patients whose transfusion status (dependent or independent) changed (from dependent to independent or vice versa) (Gale 2011) at each visit will be tabulated with summary statistics.

- **Transfusion dependence at Baseline** will be defined as patient who received 2 or more units of red blood cell product(s) during the 12 weeks prior to first study treatment administration.
- **New onset of transfusion dependence** will be defined as the use of 2 or more units of red blood cell product(s) during the last 12 weeks prior to end of study for patients who were not transfusion dependent at Baseline.
- **New transfusion independency** will be defined as no (0) use of red blood cell product(s) during the last 12 weeks prior to end of study for patients who met the definition of transfusion dependence at Baseline.

[redacted]

- **Prior and concomitant mediations**, as listed in protocol (Appendix IX) will be summarized. Concomitant medications at week 24, as listed in protocol (Appendix IX), will be summarized.

### 11.6.5 Quality of Life Assessments

The ECOG performance score will be summarized descriptively by visit. The summary will include the number and percent of patients at each reported value. A shift summary including the number and percent of patients will also be produced by visit for baseline vs. post-baseline scores.

Data from FACT-Lymphoma version 4 Scores will be analyzed in the sum scores. Change and percent change from baseline to each scheduled visit when the FACT-Lymphoma version 4 scores were collected will be calculated with the data collect from the last visit prior to and at Day 1 as the baseline. The scores will be summarized descriptively by visit.

The treatment effect on FACT-Lymphoma version Scores over time will be estimated using repeated measurements analysis including all patients with at least one post-baseline scale score. Patients without baseline value will not be considered in the analysis.

Data from FACIT Fatigue Scores will be analyzed in the sum scores. Change and percent change from baseline to each scheduled visit when the FACIT Fatigue scores were collected will be calculated with the data collect from the last cycle prior to and at Day 1 as the baseline. The scores will be summarized descriptively by visit.

Time to improvement and proportion of patients showing improvement will be estimated for ECOG performance score and for selected scales for FACT-Lymphoma version 4 and FACIT scale according to minimally important difference (MID) specified for each instrument.

### 11.6.6 Pharmacokinetics

Not applicable.

### 11.6.7 Biomarkers

Not applicable.

[redacted]

## 11.7 Interim analysis

An interim analysis will be performed to closely monitor safety, and ensure an appropriate risk/benefit ratio in the patient population with low platelet counts, between 50,000 and 100,000/μL. In order to adequately assess the risk/benefit ratio, this analysis will also be performed on non-low platelet patients (≥100,000/μL), which will be further detailed in analysis plan, who will serve as an internal reference population. This interim analysis will take place when 50 patients with low platelets have completed 6 months of treatment.

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Analyses may be performed if needed to fulfill regulatory obligations, to comply with post-approval commitments or for publication purposes.

### 11.8 Sample size calculation

This is an expanded access study and thus no sample size and no power computation was performed. The maximum number of patients that will be treated in this study is up to 2500 and is based on country assessments of the number of potential patients.

### 11.9 Power for analysis of critical secondary variables

Not applicable.

## 12 Ethical considerations and administrative procedures

### 12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the protocol, 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.

### 12.2 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 Novartis 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 Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs and regulatory authorities as required.

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

### 12.3 Informed Consent

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

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patient. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). In cases where the patient's legally acceptable representative gives consent, the patient (e.g., minors, patients with severe dementia), should be informed about the trial to the extent compatible with the patient's understanding and if capable, the patient should assent, sign and personally date the written informed consent. The process of obtaining informed consent should be documented in the patient source documents. In emergency situations when prior consent of the patient is not possible and the patient's legally acceptable representative is not available, enrollment of the patient should require measures described in the protocol with documented favorable opinion of the IRB/IEC/REB. The patient or the patient's legally appointed representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate should be requested.

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

## 12.4 Discontinuation of the study

Novartis reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 4.2.

## 12.5 Publication of study protocol and results

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

## 12.6 Study documentation, record keeping and retention of documents

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

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or

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evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial.

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

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

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

## 12.7 Confidentiality of study documents and patient records

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

## 12.8 Audits and inspections

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

## 12.9 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.

## 12.10 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the study to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by

[redacted]

Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## 12.11 Amendments to the Protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC/REB at the study site should be informed within 10 working days.

[redacted]

# 13 References (available upon request)

Abdel-Wahab OI, Levine RL (2009) Primary myelofibrosis: update on definition, pathogenesis, and treatment. Annu Rev Med;60:233-245.

Arana-Yi C, Quintas-Cardama A, Giles F, et al (2006) Advances in the therapy of chronic idiopathic myelofibrosis. Oncologist;11:929-943.

Barosi G, Bergamaschi G, Marchetti M, et al (2007) JAK2 V617F mutational status predicts progression to large splenomegaly and leukemic transformation in primary myelofibrosis. Blood;110:4030-4036.

Barosi G, Birgegard G, Finazzi G, et al (2009b) Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. Blood;113:4829-4833.

Barosi G, Birgegard G, Finazzi G, et al (2010) A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythaemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. Br J Haematol;148:961-963.

Barosi G, Mesa RA, Thiele J, et al (2008) 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. Leukemia;22:437-438.

Barosi G, Rosti V (2009a) Novel strategies for patients with chronic myeloproliferative disorders. Curr Opin Hematol;16:129-134.

Basquiera AL, Soria NW, Ryser R, et al (2009) Clinical significance of V617F mutation of the JAK2 gene in patients with chronic myeloproliferative disorders. Hematology;14:323-330.

Birgegard G (2009) Long-term management of thrombocytosis in essential thrombocythaemia. Ann Hematol;88:1-10.

Briere JB (2007) Essential thrombocythemia. Orphanet J Rare Dis;2:1-17.

Campbell PJ, Scott LM, Buck G, et al (2005) Definition of subtypes of essential thrombocythaemia and relation to polycythaemia vera based on JAK2 V617F mutation status: a prospective study. Lancet;366:1945-1953.

Cella D, Webster K, Cashy J, et al (2005) Development of a measure of health-related quality of life for non-Hodgkin's Lymphoma clinical research: the Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym). Blood;106(11):750.

Cella DF, Eton DT, Lai JS, et al (2002) Combining anchor and distribution-based methods to derive minimal clinically important differences on the functional assessment of cancer therapy (FACT) anaemia and fatigue scales. J Pain Symptom Manage; 24:547-561.

Cella DF, Tulsky DS, Gray G, et al (1993) The Functional Assessment of Cancer Therapy (FACT) scale: Development and validation of the general measure. J Clin Oncol;11:570-579.

[redacted]

Cervantes F, Dupriez B, Pereira A, et al (2009) New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood;113:2895-2901.

Chandran V, Bhella S, Schentag C, et al (2007) Functional Assessment of Chronic Illness Therapy-Fatigue Scale is valid in patients with psoriatic arthritis. Ann Rheum Dis;66(7): 936-939.

Flockhart DA (2007) Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007).Available from: http://medicine.iupui.edu/clinpharm/ddis/table.asp.> (Accessed 25 Jan 2011).

Gale R, et al (2011) What are RBC-transfusion-dependence and -independence? Leukemia Res;35:8-11.

Gangat et al (2011) DIPSS Plus: A Refined Dynamic International Prognostic Scoring System for Primary Myelofibrosis That Incorporates Prognostic Information From Karyotype, Platelet Count, and Transfusion Status. JCO February 1, 2011 vol. 29 no. 4 392-397.

Ghoreschi K, Laurence A, O'Shea JJ (2009) Janus kinases in immune cell signaling. Immunol Rev;228:273-287.

Girodon F, Bonicelli G, Schaeffer C, et al (2009) Significant increase in the apparent incidence of essential thrombocythemia related to new WHO diagnostic criteria: a population-based study. Haematologica;94:865-869.

Gisslinger H, McMullin MF, Jakel N, et al. Phase 1b, open-label, dose-finding study of ruxolitinib in patients with myelofibrosis and baseline platelet counts between 50 and ≤ 99 × $10^9$/L. Haematologica. 2012;97. Abstract 369.

Guglielmelli et al (2014a) The number of prognostically detrimental mutations and prognosis in primary myelofibrosis: an international study of 797 patients. Leukemia (2014), 1–7.

Guglielmelli et al (2014b) Impact of mutational status on outcomes in myelofibrosis patients treated with ruxolitinib in the COMFORT-II study. Blood, 3 April 2014 x Volume 123, Number 14: 2157-2160

Harrison C, Kiladjian KK, Al-Ali HK, et al (2012) JAK inhibition with INC424 versus best available therapy for myelofibrosis. N Engl J Med;366:787-798.

Harrison C, Niederwieser D, et al (2012). Anemia and the Use of Erythropoietic-Stimulating Agents (ESAs) With Ruxolitinib in the COMFORT-II Study. Poster Presentation at the 17th Congress of EHA; June 14-17, 2012; Amsterdam, The Netherlands.

Harrison C, Gisslinger H, Miller CB, et al (2012). Expand : a phase 1B, open-label, dose-finding study of ruxolitinib in patients with myelofibrosis and baseline platelet counts between 50 x $10^9$/L and 99 x $10^9$/L. Blood.120(21): Abstract 177

Incyte Corporation. Investigator's Brochure INC424 Phosphate Capsules/Tablets, Version 8, September 2009.

[redacted]

Johansson P (2006) Epidemiology of the myeloproliferative disorders polycythemia vera and essential thrombocythemia. Semin Thromb Hemost;32:171-173.

Kilpivaara, Levine (2008) JAK2 and MPL mutations in myeloproliferative neoplasms: discovery and science. Leukemia (2008) 22, 1813–1817.

Klampfl et al (2008) Somatic Mutations of Calreticulin in Myeloproliferative Neoplasms. N Engl J Med 2013;369:2379-90.

Kroger (2008) Epigenetic Modulation and Other Options to Improve Outcome of Stem Cell Transplantation in MDS. Hematology 2008: 60-67.

Landolfi R, Nicolazzi MA, Porfidia A, et al (2010) Polycythemia vera. Intern Emerg Med. 2010 March 16. [Epub ahead of print]

Levine RL, Gilliland DG (2008) Myeloproliferative disorders. Blood;112:2190-2198.

Levine RL, Heaney M (2008) New advances in the pathogenesis and therapy of essential thrombocythemia. Hematology Am Soc Hematol Educ Program;200876-82.

Mesa RA, Niblack J, Wadleigh M, et al (2007). The Burden of Fatigue and Quality of Life in Myeloproliferative Disorders (MPDs). Cancer; 109:68-76.

Mesa RA (2009a) How I treat symptomatic splenomegaly in patients with myelofibrosis. Blood;113:5394-5400.

Mesa RA (2010) New drugs for the treatment of myelofibrosis. Curr Hematol Malig Rep;5:15-21.

Mesa RA, Kantarjian H, Tefferi A, et al (2009b) Validation of the serial use of the Myelofibrosis Symptom Assessment Form (MF-SAF) for measuring symptomatic improvement: performance in 86 myelofibrosis patients on INCB018424 Clinical Trial. Blood;114:3917.

Mesa RA, Kantarjian H, Tefferi A, et al (2009c) Functional assessment of performance status in patients with myelofibrosis (MF): utility and feasibility of the 6-minute walk test (6MWT). J Clin Oncol (Meeting Abstracts);27(15S):7083.

Mesa RA, Li CY, Ketterling RP, et al (2005) Leukemic transformation in myelofibrosis with myeloid metaplasia: a single-institution experience with 91 cases. Blood;105:973-977.

Mesa RA, Niblack J, Wadleigh M, et al (2007) The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. Cancer;109:68-76.

Mesa RA, Tefferi A (2009d) Emerging drugs for the therapy of primary and post essential thrombocythemia, post polycythemia vera myelofibrosis. Expert Opin Emerg Drugs;14:471-479.

Mesa RA, Verstovsek S, Rivera C, et al (2009e) 5-Azacitidine has limited therapeutic activity in myelofibrosis. Leukemia;23:180-182.

[redacted]

National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v3.0 (CTCAE) online at NCI website:August 9, 2006 http://ctep.cancer.gov/reporting/ctc.html.

National Comprehensive Cancer Network (2012) NCCN Clinical Practice Guidelines in Oncology™: myelodysplastic syndromes. 2012;v1.2012:1-48.

Oh ST, Simonds EF, Jones C, et al (2010) Novel mutations in the inhibitory adaptor protein LNK drive JAK-STAT signaling in patients with myeloproliferative neoplasms. Blood;116:988-992.

Oken MM, Creech RH, Tormey DC, et al (1982) Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol;5:649-655.

Olcaydu D, Harutyunyan A, Jager R, et al (2009) A common JAK2 haplotype confers susceptibility to myeloproliferative neoplasms. Nat Genet;41:450-454.

Pardanani A, Lasho TL, Finke C, et al (2007) Prevalence and clinicopathologic correlates of JAK2 exon 12 mutations in JAK2V617F-negative polycythemia vera. Leukemia;21:1960-1963.

Passamonti F, Rumi E, Caramella M, et al (2008) A dynamic prognostic model to predict survival in post-polycythemia vera myelofibrosis. Blood;111:3383-3387.

Passamonti F, Rumi E, Pungolino E, et al (2004) Life expectancy and prognostic factors for survival in patients with polycythemia vera and essential thrombocythemia. Am J Med;117:755-761.

Patnaik MM, Lasho TL, Finke CM, et al (2010) WHO-defined 'myelodysplastic syndrome with isolated del(5q)' in 88 consecutive patients: survival data, leukemic transformation rates and prevalence of JAK2, MPL and IDH mutations. Leukemia;24:1283-1289.

Quintas-Cardama A, Kantarjian H, Manshouri T, et al (2009) Pegylated interferon alfa-2a yields high rates of hematologic and molecular response in patients with advanced essential thrombocythemia and polycythemia vera. J Clin Oncol;27:5418-5424.

Quintas-Cardama A, Tong W, Kantarjian H, et al (2008) A phase II study of 5-azacitidine for patients with primary and post-essential thrombocythemia/polycythemia vera myelofibrosis. Leukemia;22:965-970.

Quintas-Cardama A, Vaddi K, Liu P, et al (2010) Preclinical characterization of the selective JAK1/2 inhibitor INCB018424: therapeutic implications for the treatment of myeloproliferative neoplasms. Blood;115:3109-3117.

Rollison DE, Howlader N, Smith MT, et al (2008) Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. Blood;112:45-52.

Schafer AI (2006) Molecular basis of the diagnosis and treatment of polycythemia vera and essential thrombocythemia. Blood;107:4214-4222.

Schnittger S, Bacher U, Haferlach C, et al (2009) Detection of JAK2 exon 12 mutations in 15 patients with JAK2V617F negative polycythemia vera. Haematologica;94(3):414-418.

[redacted]

Scott LM, Tong W, Levine RL, et al (2007) JAK2 exon 12 mutations in polycythemia vera and idiopathic erythrocytosis. N Engl J Med;356:459-468.

Shilling AD, Nedza FM, Emm T, et al (2010) Metabolism, excretion and pharmacokinetics of $^{14}$C-INC424, a selective JAK1/2 inhibitor in human. Drug Metab Dispos;Aug 10 [Epub ahead of print].

Smith CA, Fan G (2008) The saga of JAK2 mutations and translocations in hematologic disorders: pathogenesis, diagnostic and therapeutic prospects, and revised World Health Organization diagnostic criteria for myeloproliferative neoplasms. Hum Pathol;39:795-810.

Spivak JL (2002) Polycythemia vera: myths, mechanisms, and management. Blood;100:4272-4290.

Spivak JL, Silver RT (2008) The revised World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytosis, and primary myelofibrosis: an alternative proposal. Blood;112:231-239.

Stuart BJ, Viera AJ (2004) Polycythemia vera. Am Fam Physician;69:2139-2144.

Swerdlow SH, Campo E, Harris NL, et al. (2008) WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC.

Talpaz M, Hamburg S, Jamieson K et al (2012). Preliminary safety and efficacy from a Phase II study of ruxolitinib in patients with primary and secondary myelofibrosis with platelet counts of 50–100 x$10^9$/L. Haematologica. Abstract 0597.

Talpaz M, Paquette R, Afrin L, et al (2012). Efficacy, hematologic effects, and dose of ruxolitinib in myelofibrosis patients with low starting platelet counts (50 – 100 x $10^9$/L): a comparison to patients with normal or high starting platelet counts. Blood. 120(21): Abstract 176.

Tefferi A (2003) Polycythemia vera: a comprehensive review and clinical recommendations. Mayo Clin Proc;78:174-194.

Tefferi A (2008) Essential thrombocythemia, polycythemia vera, and myelofibrosis: current management and the prospect of targeted therapy. Am J Hematol;83:491-497.

Tefferi A (2010a) Allogeneic hematopoietic cell transplantation versus drugs in myelofibrosis: the risk-benefit balancing act. Bone Marrow Transplant;45:419-421.

Tefferi A (2010b) Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. Leukemia;24:1128-1138.

Tefferi A, Barosi G, Mesa RA, et al (2006) International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). Blood;108:1497-1503.

Tefferi A, Huang J, Schwager S, et al (2007a) Validation and comparison of contemporary prognostic models in primary myelofibrosis: analysis based on 334 patients from a single institution. Cancer;109:2083-2088.

[redacted]

Tefferi A, Lasho TL, Mesa RA, et al (2007b) Lenalidomide therapy in del(5)(q31)-associated myelofibrosis: cytogenetic and JAK2V617F molecular remissions. Leukemia;21:1827-1828.

Tefferi A, Skoda R, Vardiman JW (2009a) Myeloproliferative neoplasms: contemporary diagnosis using histology and genetics. Nat Rev Clin Oncol;6:627-637.

Tefferi A, Strand JJ, Lasho TL, et al (2007c) Bone marrow JAK2V617F allele burden and clinical correlates in polycythemia vera. Leukemia;21:2074-2075.

Tefferi A, Verstovsek S, Barosi G, et al (2009b) Pomalidomide is active in the treatment of anemia associated with myelofibrosis. J Clin Oncol;27:4563-4569.

Thiele J, Kvasnicka HM (2005) Diagnostic impact of bone marrow histopathology in polycythemia vera (PV). Histol Histopatho;20:317-328.

Vainchenker W, Dusa A, Constantinescu SN (2008) JAKs in pathology: role of Janus kinases in hematopoietic malignancies and immunodeficiencies. Semin Cell Dev Biol;19:385-393.

Vannucchi et al (2015) A pooled analysis of overall survival in COMFORT-I and COMFORT-II, 2 randomized phase 3 trials of ruxolitinib for the treatment of myelofibrosis. Haematologica June 11, 2015.

Vannucchi AM, Antonioli E, Guglielmelli P, et al (2007) Prospective identification of high-risk polycythemia vera patients based on JAK2(V617F) allele burden. Leukemia;21:1952-1959.

Vardiman JW, Thiele J, Arber DA, et al (2009) The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood;114:937-951.

Verstovsek S, Mesa R, Gotlib J, et al (2012) A double-blind, placebo-controlled trial of INC424 for myelofibrosis. N Engl J Med;366:799-807.

Verstovsek S (2010a) Therapeutic potential of Janus-activated kinase-2 inhibitors for the management of myelofibrosis. Clin Cancer Res;16:1988-1996.

Verstovsek S, Kantarjian H, Mesa R, et al (2010b) Safety and efficacy of INCB018424, an oral JAK1 and JAK2 inhibitor, in patients with primary, post-polycythemia vera, or post-essential thrombocythemia myelofibrosis. N Engl J Med.363L1117-1127.

Verstovsek S, Kantarjian H, Mesa RA, et al (2009b) Long-term follow up and optimized dosing regimen of INCB018424 in patients with myelofibrosis: durable clinical, functional and symptomatic responses with improved hematological safety. Blood;114:756.

Verstovsek S, Passamonti F, Rambaldi A, et al (2009a) A phase 2 study of INCB018424, an oral, selective JAK1/JAK2 inhibitor, in patients with advanced polycythemia vera (PV) and essential thrombocythemia (ET) refractory to hydroxyurea. Blood;114:311.

Wolanskyj AP, Schwager SM, McClure RF, et al (2006) Essential thrombocythemia beyond the first decade: life expectancy, long-term complication rates, and prognostic factors. Mayo Clin Proc;81:159-166.

[redacted]

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000. Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002. Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004. Available at http://wma.net/en/30publications/10policies/b3/index.html.

[redacted]

# 14 Appendices

## 14.1 Appendix I - Diagnostic criteria for PMF, PPV MF, and PET-MF

| **Criteria for post-polycythemia vera myelofibrosis (Barosi 2008)** |
|---|
| **Required criteria:**<br>1. Documentation of a previous diagnosis of polycythemia vera as defined by the WHO criteria (Tefferi 2007d)<br>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):**<br>1. Anemia[b] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis<br>2. A leukoerythroblastic peripheral blood picture<br>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<br>4. Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5ºC) |
| [a]Grade 2–3 according to the European classification:<br>[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).<br>Grade 3–4 according to the standard classification:<br>[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.<br>[b]Below the reference range for appropriate age, sex, gender and altitude considerations. |

| **Criteria for post-essential thrombocythemia myelofibrosis (Barosi 2008)** |
|---|
| **Required criteria:**<br>1. Documentation of a previous diagnosis of essential thrombocythemia as defined by the WHO criteria (Tefferi 2007d)<br>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):**<br>1. Anemia[b] and a ≥2mg $ml^{-1}$ decrease from baseline hemoglobin level<br>2. A leukoerythroblastic peripheral blood picture<br>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<br>4. Increased LDH (above reference level)<br>5. Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (> 37.5ºC) |
| [a]Grade 2–3 according to the European classification:<br>[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).<br>Grade 3–4 according to the standard classification:<br>[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.<br>[b]Below the reference range for appropriate age, sex, gender and altitude considerations. |

[redacted]

## Diagnostic criteria for polycythemia vera essential thrombocythemia, and primary myelofibrosis (Swerdlow 2008, Vardiman 2009)

### Criteria for the diagnosis of polycythemia vera (PV)

| **Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria** |
|---|
| **Major Criteria** |
| Hemoglobin > 18.5 g/dL in men; 16.5 g/dL in women or other evidence of increased red cell volume*<br>Presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation |
| **Minor Criteria** |
| Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation<br>Serum erythropoietin level below the reference range for normal<br>Endogenous erythroid colony formation in vivo |
| * Hemoglobin or hematocrit > 99$^{th}$ percentile of method-specific reference range for age, sex, altitude of residence or hemoglobin > 17g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from a person's baseline value that cannot be attributed to correction of iron deficiency or elevated red cell mass > 25% above mean normal predicted value. |

### Criteria for the diagnosis of essential thrombocythemia (ET)

| **Diagnosis requires meeting all four criteria** |
|---|
| 1. Sustained platelet count ≥ 450 x 109/L*<br>2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes. No significant increase or left-shift of neutrophil granulopoiesis or erythropoiesis.<br>3. Not meeting WHO criteria for polycythemia vera,† primary myelofibrosis,‡ BCR-ABL1-positive CML,§ or myelodysplastic syndrome,‖ or other myeloid neoplasm.<br>4. Demonstration of JAK2 V617F or other clonal marker, or in the absence of JAK2 V617F, no evidence of reactive thrombocytosis¶. |
| ET indicates essential thrombocythemia; BM, bone marrow; WHO, World Health Organization; and CML, chronic myelogenous leukemia.<br>* Sustained during the work-up process.<br>† Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels, and red cell mass measurement is not required.<br>‡ Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis, or markedly hypercellular marrow accompanied by megakaryocyte morphology that is typical for primary myelofibrosis-small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.<br>§ Requires the absence of BCR-ABL1.<br>‖ Requires the absence of dyserythropoiesis and dysgranulopoiesis.<br>¶ Causes of reactive thrombocytosis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders. However, the presence of a condition associated with reactive thrombocytosis does not exclude the possibility of ET if other criteria are met. |

[redacted]

## Criteria for the diagnosis of primary myelofibrosis (PMF)

| **Diagnosis requires meeting all 3 major criteria and 2 minor criteria** |
|---|
| **Major Criteria** |
| 1. Presence of megakaryocyte proliferation and atypia,* usually accompanied by either reticulin or collagen fibrosis or, in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e., prefibrotic cellular-phase disease)<br>2. Not meeting WHO criteria for polycythemia vera,† BCR-ABL1-positive chronic myelogenous leukemia,‡ myelodysplastic syndrome,§ or other myeloid disorders<br>3. Demonstration of JAK2 V617F or other clonal marker (e.g., MPLW515K/L) or, in the absence of the above clonal markers, no evidence that bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies‖ |
| **Minor Criteria** |
| 1. Leukoerythroblastosis¶<br>2. Increase in serum lactate dehydrogenase level¶<br>3. Anemia¶<br>4. Palpable splenomegaly¶ |
| * Small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering.<br>† Requires the failure of iron replacement therapy to increase hemoglobin level to the polycythemia vera range in the presence of decreased serum ferritin. Exclusion of polycythemia vera is based on hemoglobin and hematocrit levels. Red cell mass measurement is not required.<br>‡ Requires the absence of BCR-ABL1.<br>§ Requires the absence of dyserythropoiesis and dysgranulopoiesis.<br>‖ It should be noted that patients with conditions associated with reactive myelofibrosis are not immune to primary myelofibrosis, and the diagnosis should be considered in such cases if other criteria are met.<br>¶ Degree of abnormality could be borderline or marked. |

[redacted]

## 14.2 Appendix II - Information regarding highly effective contraception methods

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), total 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). The vasectomized male partner should be the sole partner for that subject.
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception (in case of oral contraception you should have been using the same pill on a stable dose for a minimum of 3 months before screening)

## 14.3 Appendix III - Clinical laboratory tests

<table>
<tr><th>Serum chemistry</th><th>Hematology</th><th>Other</th></tr>
<tr><td rowspan="3">ALT<br>AST<br>Bilirubin - Total and Direct<br>Alkaline phosphatase<br>Serum Creatinine</td><td>Complete Blood Count (CBC)<br>Differential (neutrophils, lymphocytes, eosinophils, basophils, monocytes), including reporting of % blasts<br>Platelets<br>Reticulocyte count (absolute and % reticulocytes) optional</td><td rowspan="3">Serology: hepatitis A, B, and C<br>HIV Antibody<br>Pregnancy Test: Female patients of childbearing potential only. Serum test at Screening (Section 7).<br><br>Thiamine blood level (Section 7)</td></tr>
<tr><td>Coagulation (Required for screening / baseline , optional after enrollment)</td></tr>
<tr><td>PT (or INR)<br>PTT</td></tr>
<tr><td colspan="3">ALT = alanine aminotransferase, AST = aspartate aminotransferase, PT = prothrombin time, PTT = partial thromboplastin time.</td></tr>
</table>

[redacted]

## 14.4 Appendix IV - Eastern Cooperative Oncology Group 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, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead |

## 14.5 Appendix V - Bone marrow biopsy evaluation (when performed, they are not mandatory)

### Fibrosis density should be assessed in hematopoietic areas

| Fibrosis Grade | Description |
|---|---|
| 0 | Scattered linear reticulin with no intersections corresponding to normal bone marrow |
| 1 | Loose network of reticulin with many intersections, especially in perivascular areas |
| 2 | Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis |
| 3 | Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant |
| **Note**: Fibrosis density should be assessed in hematopoietic areas. Source: Tefferi (2006). | |

[redacted]

## 14.6 Appendix VI - Restricted/prohibited medications

These medications are restricted or prohibited **in combination with INC424**:

### Prohibited medications

- Aspirin > 150 mg/day
- Any other investigational medication
- Any other medication for myelofibrosis (these medications must be discontinued prior to Day 1 of INC424 treatment, and all adverse events associated with these medications must be resolved prior to Day 1 of INC424 therapy).
  - Anagrelide
  - Busulfan
  - Hydroxyurea
  - Interferon
  - Lenalidomide
  - Thalidomide

### Restricted medications

Use of all CYP3A4 inhibitors is discouraged as they may have effects on plasma levels of INC424; alternative therapies should be considered, if available

| Category | Drug Names |
|---|---|
| Strong inhibitors[a] of CYP3A | boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice[1], idelalisib, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, LCL161, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, troleandomycin, |
| Moderate inhibitors[b] of CYP3A | amprenavir, aprepitant, atazanavir, atazanavir/ritonavir,, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, duranavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, faldaprevilr, fluconazole[2], fosamprenavir, grapefruit juice[1], imatinib, lomitapide, netupitant,nilotinib, schisandra sphenanthera[3], tofisopam, verapamil |
| Strong inducers[c] of CYP3A | avasimibe, carbamazepine, enzalutamide, mitotane,phenytoin, rifampin, St. John's wort[3], rifabutin, phenobarbital, |
| Moderate inducers[d] of CYP3A | bosentan, efavirenz, etravirine, genistein[3], lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat[4], talviraline[4], thioridazine, tipranavir, , |
| The list of CYP inhibitors and inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database. Note that this may not an exhaustive list. Please refer to footnotes. | |

[redacted]

1. Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
2. Fluconazole is a dual CYP3A4 and CYP2C9 inhibitor. Fluconazole is a strong CYP2C9 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
3. Herbal product.
4. Drugs not available in the US Market.

[a]A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold.
[b]A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold
[c] A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%.
[d] A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%.

### Dual CYP2C9 and CYP3A4 inhibitors:

Fluconazole avoid the concomitant use of ruxolitinib with fluconazole doses ≥ 200 mg daily; If clinically necessary to use doses ≥ 200 mg daily consultation with Sponsor is required. Please refer to Section 6.4.2.

[redacted]

## 14.7 Appendix VII - FACT-Lym Form, Version 4

### FACT-Lym (Version 4)

**Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | PHYSICAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GP1 | I have a lack of energy | 0 | 1 | 2 | 3 | 4 |
| GP2 | I have nausea | 0 | 1 | 2 | 3 | 4 |
| GP3 | Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| GP4 | I have pain | 0 | 1 | 2 | 3 | 4 |
| GP5 | I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| GP6 | I feel ill | 0 | 1 | 2 | 3 | 4 |
| GP7 | I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| | SOCIAL/FAMILY WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GS1 | I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| GS2 | I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| GS3 | I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| GS4 | My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GS5 | I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| GS6 | I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |
| Q1 | *Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.* | | | | | |
| GS7 | I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |





[redacted]

## FACT-Lym (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | EMOTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GE1 | I feel sad | 0 | 1 | 2 | 3 | 4 |
| GE2 | I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| GE3 | I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| GE4 | I feel nervous | 0 | 1 | 2 | 3 | 4 |
| GE5 | I worry about dying | 0 | 1 | 2 | 3 | 4 |
| GE6 | I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| | FUNCTIONAL WELL-BEING | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| GF1 | I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| GF2 | My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| GF3 | I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| GF4 | I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| GF5 | I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| GF6 | I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| GF7 | I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |





[redacted]

## FACT-Lym (Version 4)

**Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | ADDITIONAL CONCERNS | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| P2 | I have certain parts of my body where I experience pain | 0 | 1 | 2 | 3 | 4 |
| LEU1 | I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin) | 0 | 1 | 2 | 3 | 4 |
| BRM3 | I am bothered by fevers (episodes of high body temperature) | 0 | 1 | 2 | 3 | 4 |
| ES3 | I have night sweats | 0 | 1 | 2 | 3 | 4 |
| LYM1 | I am bothered by itching | 0 | 1 | 2 | 3 | 4 |
| LYM2 | I have trouble sleeping at night | 0 | 1 | 2 | 3 | 4 |
| EMT6 | I get tired easily | 0 | 1 | 2 | 3 | 4 |
| C2 | I am losing weight | 0 | 1 | 2 | 3 | 4 |
| Ga1 | I have a loss of appetite | 0 | 1 | 2 | 3 | 4 |
| HS8 | I have trouble concentrating | 0 | 1 | 2 | 3 | 4 |
| N3 | I worry about getting infections | 0 | 1 | 2 | 3 | 4 |
| LEU6 | I worry that I might get new symptoms of my illness | 0 | 1 | 2 | 3 | 4 |
| LEU7 | I feel isolated from others because of my illness or treatment | 0 | 1 | 2 | 3 | 4 |
| BRM9 | I have emotional ups and downs | 0 | 1 | 2 | 3 | 4 |
| LEU4 | Because of my illness, I have difficulty planning for the future | 0 | 1 | 2 | 3 | 4 |



[redacted]

## 14.8 Appendix VIII - FACIT Fatigue Scale (Version 4)

**FACIT Fatigue Scale (Version 4)**

**Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

| | | Not at all | A little bit | Some-what | Quite a bit | Very much |
|---|---|---|---|---|---|---|
| H7 | I feel fatigued | 0 | 1 | 2 | 3 | 4 |
| H12 | I feel weak all over | 0 | 1 | 2 | 3 | 4 |
| An1 | I feel listless ("washed out") | 0 | 1 | 2 | 3 | 4 |
| An2 | I feel tired | 0 | 1 | 2 | 3 | 4 |
| An3 | I have trouble starting things because I am tired | 0 | 1 | 2 | 3 | 4 |
| An4 | I have trouble finishing things because I am tired | 0 | 1 | 2 | 3 | 4 |
| An5 | I have energy | 0 | 1 | 2 | 3 | 4 |
| An7 | I am able to do my usual activities | 0 | 1 | 2 | 3 | 4 |
| An8 | I need to sleep during the day | 0 | 1 | 2 | 3 | 4 |
| An12 | I am too tired to eat | 0 | 1 | 2 | 3 | 4 |
| An14 | I need help doing my usual activities | 0 | 1 | 2 | 3 | 4 |
| An15 | I am frustrated by being too tired to do the things I want to do | 0 | 1 | 2 | 3 | 4 |
| An16 | I have to limit my social activity because I am tired | 0 | 1 | 2 | 3 | 4 |





[redacted]

## 14.9 Appendix IX - MRU concomitant medication

Listed below are the concomitant medications for MPN symptom management that will be recorded for MRU.

| GENERIC NAME | INDICATION |
|---|---|
| ACECLOFENAC | pain |
| ACETAMINOPHEN | fever, pain |
| ACETYLSALICYLIC ACID | thrombosis prophylaxis |
| ACICLOVIR | herpes zoster |
| ALLOPURINOL | hyperuricemia |
| AMIKACIN SULFATE | bacterial infection |
| AMITRIPTYLINE | postherpetic neuralgia |
| AMOXICILLIN | bacterial infection |
| AMOXICILLIN W/CLAVULANATE | bacterial infection |
| AMPHOTERICIN B | fungal infection |
| ANAGRELIDE | thrombosis prophylaxis |
| AZTREONAM | bacterial infection |
| BIOFLAVONOIDS | thrombosis prophylaxis |
| CARBASALATE CALCIUM | thrombosis prophylaxis |
| CASPOFUNGIN | fungal infection |
| CEFEPIME | bacterial infection |
| CEFOTAXIME SODIUM | bacterial infection |
| CEFTAZIDIME | bacterial infection |
| CEFTRIAXONE | bacterial infection |
| CEFUROXIME | bacterial infection |
| CELECOXIB | pain |
| CETIRIZINE | pruritus |
| CIPROFLOXACIN | bacterial infection |
| CLARITHROMYCIN | bacterial infection |
| CLAVULANIC ACID | bacterial infection |
| CLINDAMYCIN | bacterial infection |
| CLOPIDOGREL | thrombosis prophylaxis |
| CLOTRIMAZOLE | fungal infection |
| CODEINE PHOSPHATE | pain |
| CO-TRIMOXAZOLE | bacterial infection |
| DALTEPARIN | thrombosis prophylaxis |
| DANOCRINE (Danazol®) | myelofibrosis |
| DARBEPOETIN ALFA | anemia |
| DEFERASIROX | iron overload |
| DEFEROXAMINE MESILATE | iron overload |
| DEXIBUPROFEN | pain |
| DICLOFENAC | pain |
| DIHYDROCODEINE | pain |
| DIMENHYDRINATE | nausea |
| DIMETINDENE | pruritus |

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| GENERIC NAME | INDICATION |
|---|---|
| DIPHENHYDRAMINE | pruritus |
| DIPYRIDAMOLE | thrombosis prophylaxis |
| DOXYCYCLINE | bacterial infection |
| ENOXAPARIN | thrombosis prophylaxis |
| EPOETIN ALFA | anemia |
| EPOETIN BETA | anemia |
| ERYTHROMYCIN | bacterial infection |
| ESOMEPRAZOLE | gastritis-reflux |
| ETOFENAMATE | pain |
| ETORICOXIB | pain |
| FENTANYL | pain |
| FILGRASTIM | leukopenia |
| FLUCLOXACILLIN | bacterial infection |
| FLUCONAZOLE | fungal infection |
| FUROSEMIDE | edema |
| FUSIDIC ACID | bacterial infection |
| GABAPENTIN | postherpetic neuralgia |
| GENTAMICIN | bacterial infection |
| HEPARIN | thrombosis prophylaxis |
| HYDROCHLOROTHIAZIDE | edema |
| HYDROMORPHONE HYDROCHLORIDE | pain |
| IBUPROFEN | pain |
| IMIPENEM | bacterial infection |
| INDOBUFEN | thrombosis prophylaxis |
| KETOPROFEN | pain |
| LEVOFLOXACIN | bacterial infection |
| LIDOCAINE HYDROCHLORIDE | pain |
| LINEZOLID | bacterial infection |
| LORATADINE | pruritus |
| MEFENAMIC ACID | pain |
| MEROPENEM | bacterial infection |
| METAMIZOLE | fever, pain |
| METOCLOPRAMIDE HYDROCHLORIDE | nausea |
| MINOCYCLINE HYDROCHLORIDE | bacterial infection |
| MORPHINE | pain |
| MOXIFLOXACIN | bacterial infection |
| NADROPARIN | thrombosis prophylaxis |
| NAPROXEN | pain |
| NIMESULIDE | fever, pain |
| NITROFURANTOIN | bacterial infection |
| NORFLOXACIN | bacterial infection |
| OFLOXACIN | bacterial infection |
| OMEPRAZOLE | gastritis-reflux |
| ONDANSETRON | nausea |

[redacted]

| GENERIC NAME | INDICATION |
|---|---|
| OXYCODONE | pain |
| PALONOSETRON HYDROCHLORIDE | nausea |
| PANTOPRAZOLE | gastritis-reflux |
| PARACETAMOL | fever, pain |
| PARACETAMOL W/TRAMADOL | pain |
| PETHIDINE HYDROCHLORIDE | pain |
| PHENPROCOUMON | thrombosis prophylaxis |
| PIPERACILLIN | bacterial infection |
| PIPERACILLIN/TAZOBACTAM | bacterial infection |
| PIROXICAM | pain |
| PLATELETS, CONCENTRATED | thrombocytopenia |
| PREDNISOLONE | fever prophylaxis |
| PRIMAXIN | bacterial infection |
| PRISTINAMYCIN | bacterial infection |
| PROPRANOLOL | prophylaxis of variceal bleeding |
| RANITIDINE | gastritis-reflux |
| RED BLOOD CELLS, CONCENTRATED | anemia |
| ROXITHROMYCIN | bacterial infection |
| SPIRONOLACTONE | edema |
| TICLOPIDINE | thrombosis prophylaxis |
| TOBRAMYCIN SULFATE | bacterial infection |
| TORASEMIDE | edema |
| TRAMADOL | pain |
| TRIMETHOPRIM | bacterial infection |
| VALACYCLOVIR | herpes zoster |
| VALORON N | pain |
| VANCOMYCIN HYDROCHLORIDE | bacterial infection |
| VORICONAZOLE | fungal infection |
| WARFARIN | thrombosis prophylaxis |
| XIPAMIDE | edema |

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