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Ruxolitinib (INC424)

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**A multi-national open-label phase II study of the JAK inhibitor INC424 in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis**

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## Protocol Summary

### Study title:

A multi-national open-label phase II study of the JAK inhibitor INC424 in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis

### Study phase:

Phase II

### Study objectives:

The primary objective of this study is to determine the efficacy of INC424 as assessed by reduction in spleen volume. The secondary objectives are to determine the safety and tolerability of INC424, to evaluate the effects of INC424 on patient reported outcomes and the duration of response as assessed by reduction in spleen volume.

### Study population:

Patients with primary myelofibrosis (PMF) or myelofibrosis (MF) evolving from polycythemia vera (PV) or essential thrombocythemia (ET), who have a palpable spleen measuring 5 cm or greater below the costal margin and are classified as high risk or intermediate-2 risk according to the risk stratification by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT). Patients must be 18 years of age or older with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and have adequate hematologic (absolute neutrophil count  $\geq 1,000/\mu\text{L}$  and platelet count  $\geq 100,000/\mu\text{L}$ ), renal, and hepatic function. Patients must have discontinued all drugs used to treat underlying MF no later than 28 days prior to Baseline.

### Overview of study design:

This is an Asian multi-national phase II open-label study evaluating the efficacy and safety of INC424 in patients with PMF or post-PV/ET MF. The study is comprised of 4 phases; the Screening phase, the Baseline phase, the Treatment phase, and Follow-up. After the Screening and Baseline phases, patients who meet all the eligibility criteria will start treatment with INC424. INC424 is self-administered orally, and the starting dose will be determined based on Baseline platelet count; patients with Baseline platelet count of  $100,000/\mu\text{L}$  to  $200,000/\mu\text{L}$  will begin dosing at 15 mg twice daily (BID), and those with Baseline platelet count higher than  $200,000/\mu\text{L}$  will begin dosing at 20 mg BID. A standardized dosing paradigm will be used to determine dose adjustments for safety and efficacy so that each patient is titrated to their most appropriate dose. The minimum and maximum doses will be 5 mg BID (or 5 mg once daily if used with a concomitant strong CYP3A4 inhibitor) and 25 mg BID, respectively. Patients will receive INC424 until the patients have access to treatment through commercial supplies (if applicable by local regulations) or the patients are permanently discontinued from the study, whichever comes first. A Follow-up Visit will be held 30 days after the last dose of study drug.

The primary efficacy endpoint will be based on the proportion of patients achieving  $\geq 35\%$  reduction in spleen volume from Baseline to Week 24 as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan in applicable patients. The secondary efficacy endpoints will be the changes in scores assessed both by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and by Seven-day modified Myelofibrosis Symptom Assessment Form (MFSAF) v2.0 from Baseline to Week 24, best response rate and the duration of maintenance of a  $\geq 35\%$  reduction from Baseline in spleen volume. Safety and tolerability will be assessed by monitoring the frequency, duration and severity of adverse events, performing physical exams, and evaluating changes in vital signs, electrocardiograms (ECGs), serum chemistry, hematology and urinalysis results.

The target number of patients will be 110, and an interim analysis is planned when the first 50 patients have completed Week 24 Visit or have discontinued from the study prior to Week 24.

**Statistical considerations:**


The sample size for this study is based on the single-sample binomial test (normal approximation). Based on the results obtained in Study INCB 18424-351, the proportion of patients on this study achieving  $\geq 35\%$  reduction in spleen volume from Baseline to Week 24 as measured by MRI (or CT scan) is expected to be 0.35. From the aspect of clinical benefit in patients with PMF or post-PV/ET MF, a threshold of 0.2 was set for null hypothesis. If the study had no interim analysis (1-stage approach), the required sample size of 110 provides power of 0.951 with one-sided type I error rate of 0.025 under response rate of 0.2 and 0.35 for null and alternative hypotheses. The power for the group sequential (i.e. 2-stage) design accruing 110 total patients with the same final timepoint boundary ( $\geq 31/110$ ) and an interim analysis conducted after 50 patients using an O'Brien-Fleming type interim analysis boundary ( $\geq 19/50$ ) is approximately 0.95. Therefore, the effect of the interim analysis on the overall study power is negligible.

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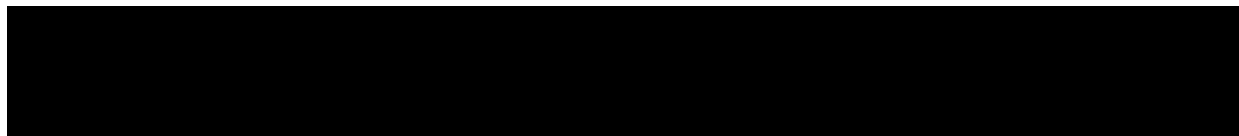


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## List of abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANC	Absolute neutrophil count
AUC	Area under the plasma concentration-time curve
BDM	Biometrics and Data Management
BID	Bis in diem (Twice daily)
BMI	Body mass index
C <sub>max</sub>	Maximum observed plasma concentration
CRO	Contract Research Organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DMC	Data Monitoring Committee
DLT	Dose limiting toxicity
DS&E	Drug Safety and Epidemiology
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ET	Essential thrombocythemia
FAS	Full analysis set
GCP	Good Clinical Practice
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
IB	Investigator's Brochure
IC <sub>50</sub>	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IN	Investigator Notification
INC424	INCB018424, ruxolitinib
INR	International normalized ratio
IRB	Institutional Review Board
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
JAK	Janus kinase
LLOQ	Lower limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MF	Myelofibrosis

MFSAF	Myelofibrosis Symptom Assessment Form
MPN	Myeloproliferative neoplasm
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
PAS	Pharmacokinetic Analysis Set
PD	Pharmacodynamic(s)
PHI	Protected health information
PK	Pharmacokinetic(s)
PMF	Primary myelofibrosis
PPS	Per-protocol Set
PT	Prothrombin time
PTT	Partial thromboplastin time
PV	Polycythemia vera
QD	Quaque die (Once daily)
QOL	Quality of life
QTcF	QT interval corrected according to Friderica's formula
RAP	Report and Analysis plan
REB	Research Ethics Board
SAE	Serious adverse event
SAF	Safety population
SC	Steering Committee
SEC	Safety event category
STAT	Signal transducers and activators of transcription
SUSAR	Suspected unexpected serious adverse reactions
$t_{1/2}$	Elimination half life
TNF- $\alpha$	Tumor Necrosis Factor $\alpha$
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

## 1 Background

### 1.1 Overview of pathogenesis, epidemiology and current treatments of myelofibrosis

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) originating from a clonal hematopoietic stem cell. MF can present as primary myelofibrosis (PMF) or evolve from underlying polycythemia vera (PV) or essential thrombocythemia (ET). Regardless of whether MF develops as PMF or from PV or ET, it is characterized by a clonal stem cell proliferation associated with production of elevated levels of several inflammatory cytokines, which causes collagen fibrosis in the bone marrow. The abnormal bone marrow milieu results in release of hematopoietic stem cells into the blood, extramedullary hematopoiesis, and organomegaly at these sites. The incidence of PMF has been estimated at 0.5 to 1.5 cases per 100,000 people, and it occurs most commonly in the sixth to seventh decade of life ([Thiele et al. 2008](#)). Clinically, MF is characterized by progressive anemia, massive splenomegaly due to extramedullary hematopoiesis, severe constitutional symptoms, a hypermetabolic state, cachexia, and premature death. The most common causes of death are progressive marrow failure leading to infection or hemorrhage, and transformation to acute leukemia.

Recently, a gain-of-function mutation in the Janus kinase-2 (JAK2) gene, specifically 1849G>T (encoding V617F), has been identified in over 95% of patients with PV and 60% of patients with ET and PMF ([Vannucchi et al. 2009](#)). JAK2 is a member of the JAK family kinases, a non-receptor tyrosine kinase associated with signal transductions of a considerable number of cytokines and growth factors ([Levine et al. 2007](#)). For example, erythropoietin, thrombopoietin and granulocyte macrophage colony stimulating factor are all known to signal through receptors that utilize JAK2. 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. Cumulative evidence has revealed that JAK2 plays a critical role in the pathogenesis of MPN by activating a number of downstream pathways involved in the proliferation and survival of malignant cells such as STAT (signal transducers and activators of transcription). It was shown that also in patients lacking a confirmed JAK2 mutation, STAT is activated suggesting dysregulated JAK activity regardless of the JAK2 mutation status ([Verstovsek et al. 2010](#)).

Survival in MF varies with the presence or absence of specific risk factors including age of greater than 65 years, presence of constitutional symptoms of weight loss, fever, or night sweats, anemia (hemoglobin [Hgb] less than 10 g/dL), leukocytosis (white blood cell [WBC] greater than 25,000/ $\mu$ L), and a circulating blast percentage of 1% or greater. It was demonstrated that patients with no risk factors fell into a low risk group with a median survival of approximately 11 years, patients with one risk factor fell into an intermediate-1 risk group with a median survival of approximately 8 years, patients with two risk factors fell within an intermediate-2 risk group with a median survival of 48 months, and patients with 3 or more risk factors formed a high risk group with a median survival of 27 months ([Cervantes et al. 2009](#)).

Currently, there are no curative therapies for MF except for allogeneic hematopoietic stem cell transplantation (HSCT). Allogeneic HSCT may provide a cure, although it is only

applicable to a small fraction of patients who are young and fit for the procedure and have a suitable donor. Moreover, allogeneic HSCT is associated with a considerable risk of treatment-related morbidity and mortality. Other therapeutic options include hydroxyurea, busulfan, 6-mercaptopurine, anagrelide, thalidomide, lenalidomide, interferon, corticosteroids, androgens, hematopoietic growth factors, splenectomy, and splenic irradiation, none of which has been shown to improve survival (Kroger et al. 2008). Even if symptom control is successfully achieved with these treatments, response is not durable.

## **1.2 Introduction to investigational treatment**

### **1.2.1 Overview of INC424**

INCB018424 phosphate designated INC424 throughout, represents a novel, potent, reversible and selective inhibitor of JAK1- and JAK2-STAT signaling pathways, and is currently under development for treatment of MPN.

#### **1.2.1.1 Non-clinical experience**

INC424 potently inhibits JAK1 and JAK2 (half maximal inhibitory concentration [ $IC_{50}$ ] 0.4 to 1.7 nM), yet it does not significantly inhibit (<30% inhibition) a broad panel of 28 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. INC424 retains activity against the JAK2V617F mutant and is effective in reducing splenomegaly in mice inoculated with cells carrying this mutation.

Effects of INC424 noted in 6-month rat and 12-month dog repeat dose toxicology studies were primarily myelosuppressive in nature and are believed to be associated with the mechanism of action of INC424. Genetic toxicology assessments (evaluations of INC424 in the bacterial mutagenicity assay, *in vitro* chromosome aberration assay, and *in vivo* micronucleus assay) in rats were negative. In safety pharmacology evaluations, an adverse decrease in minute volume in a respiratory study in female rats only was noted at the highest dose. In a cardiovascular evaluation of INC424 in dogs, electrocardiogram (ECG) parameters and ventricular repolarization were unaffected at all doses; whereas the compound lowered blood pressure and increased heart rate compared to vehicle control at the highest dose evaluated. In embryo-fetal assessments in rat and rabbit, maternal toxicity and minimal embryo-fetal toxicity were noted at the highest doses evaluated. INC424 was not teratogenic in either rat or rabbit. No effects were noted on reproductive performance or fertility in male or female rats. Increases in post-implantation loss were noted at the higher doses.

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

#### **1.2.1.2 Clinical experience**

##### **Clinical Pharmacology**

Following oral, single-dose administration in the fasted state, INC424 was absorbed rapidly, typically attaining peak plasma concentrations within 1 to 3 hours after administration for all

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

INC424 is metabolized in the liver by the cytochrome (CYP) P450 metabolizing enzyme system, predominantly by the 3A4 isozyme. Systemic exposure of INC424 was appreciably increased (AUC 2-fold higher) when given in combination with ketoconazole, a potent CYP3A4 inhibitor, with a similar effect observed on the pharmacodynamic (PD) activity (cytokine-induced STAT3 phosphorylation). CYP3A4 inducers significantly decreased the exposure to INC424, with essentially no difference observed on the PD activity. This suggests that CYP3A4 induction with rifampin results in metabolism of INC424 to active metabolites which also inhibit JAKs.

INC424 was given as a single 25 mg dose to subjects with varying degrees of renal function (Study [INCB 18424-142]) and to subjects with varying degrees of hepatic dysfunction or with normal hepatic function (Study [INCB 18424-137]). Mild, moderate or severe impairment of renal function had no statistically significant effect on pharmacokinetic (PK) or PD parameters; subjects requiring dialysis showed prolonged PD activity without a demonstrable effect on INC424 clearance. The mean total AUCs of INC424 were 88%, 29% and 66% higher, respectively, in subjects with mild, moderate and severe hepatic impairment compared to subjects with normal hepatic function. INC424  $C_{max}$  was not significantly different for subjects with various degrees of hepatic impairment compared with healthy subjects following single-dose administration. Terminal half-life of INC424 was increased in subjects with hepatic impairment by approximately 2-fold compared to healthy controls. The subjects with severe hepatic impairment showed modestly protracted PD activity compared to the other hepatically impaired subjects who displayed PD activity similar to the healthy controls.

In addition to these studies conducted in western countries, the pharmacokinetics of INC424 in Japanese healthy volunteers was recently investigated (Study [CINC424A1101]). Following oral administration to Japanese healthy volunteers, INC424 was rapidly absorbed, and peak plasma concentrations were reached 0.5 hours after dose administration. Exposure of INC424 increased proportionately with dose. The short half life (2-3 hours) relative to the 12 hour dose interval is consistent with no accumulation observed after multiple dosing.

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

### **Clinical Safety in Healthy Volunteers**

INC424 has been administered in single or multiple doses to over 130 western healthy subjects. In single dose studies, INC424 has been safe and well tolerated with adverse events generally mild in intensity, reversible and of similar incidence following INC424 treatment compared with placebo or with other control treatments.

In a 10-day multiple dose study, a total of 71 healthy volunteers in 6 cohorts received doses of 50 mg once daily (QD), 100 mg QD, 15 mg twice daily (BID), 25 mg BID or 50 mg BID INC424 or placebo (Study [\[INCB 18424-132\]](#)). INC424 was well tolerated in the study, with most adverse events reported equally by both INC424-treated and placebo-treated subjects. Neutropenia was noted in 3 subjects receiving the highest dose of INC424, 50 mg BID. Neutropenia at the Grade 4 level led to study drug discontinuation on Day 5 in one subject and was reported as a serious adverse event (SAE). There was a decline in mean absolute neutrophil count (ANC) values and to a lesser extent, mean WBC values, with INC424 doses of 15 mg BID or higher. In general ANC or WBC returned to Baseline levels within 1 to 2 days following the last dose of study drug. Doses of 25 mg BID was determined to be the maximum tolerated doses (MTD) in this study based on the dose limiting toxicity (DLT) of neutropenia. Doses of 50 mg QD and 100 mg QD were well tolerated.

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

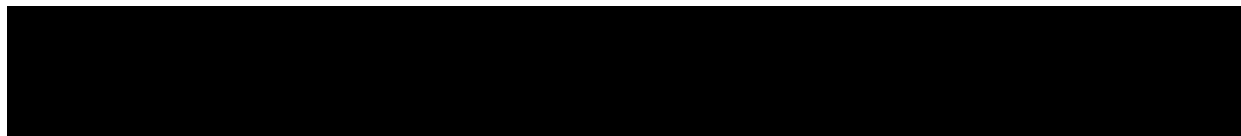
In the phase I study with Japanese healthy volunteers (Study [\[CINC424A1101\]](#)), INC424 was found to be well tolerated up to 100 mg single-dosing as well as 25 mg BID multiple-dosing for 7 days.

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

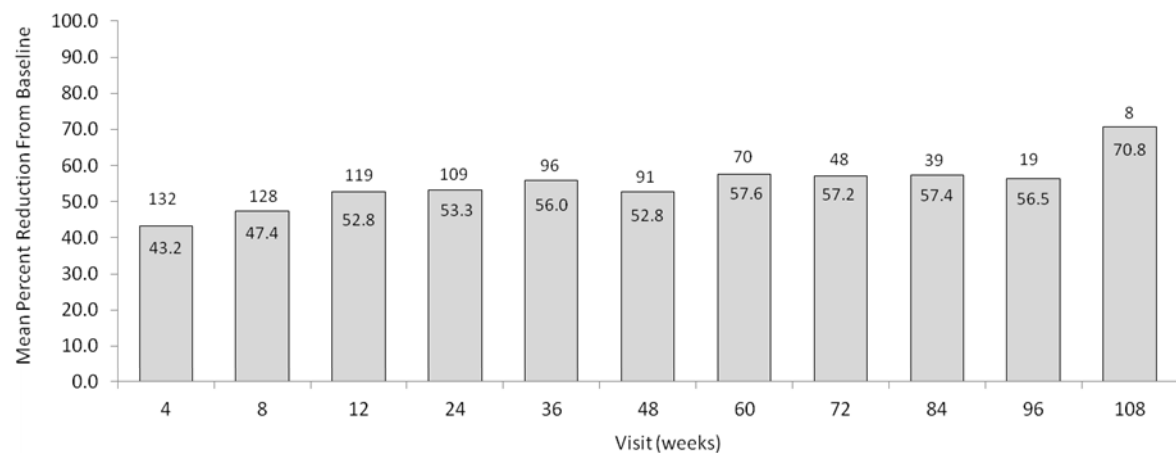
### **Clinical Safety and Efficacy in MF Patients**

Study [\[INCB 18424-251\]](#) is a phase I/II open-label study of INC424 in patients with PMF or post-PV/ET MF. As of December 31, 2009, 154 patients have been enrolled at twice daily dose regimens of 10 mg BID to 50 mg BID, or once daily regimens of 25 mg QD to 200 mg QD. Patients enrolled since August 2008 have had individually titrated dose regimens that begin at doses of 10 mg BID or 15 mg BID, and can increase up to 20 mg BID or 25 mg BID.

Data from the ongoing Study [\[INCB 18424-251\]](#) demonstrate marked and durable reductions in spleen size. In this study, spleen size has been measured as palpable length below the left costal margin. [Figure 1-1](#) illustrates the mean reduction in absolute spleen size (measured from the costal margin) for all participants in the study.



**Figure 1-1 Mean reduction in palpable spleen length in Study INCB 18424-251**



The numbers above the bar graphs are the denominators of how many individuals were followed for that period of time, and the numbers in the bar graphs are the percentage reduction in palpable spleen length compared with Baseline.

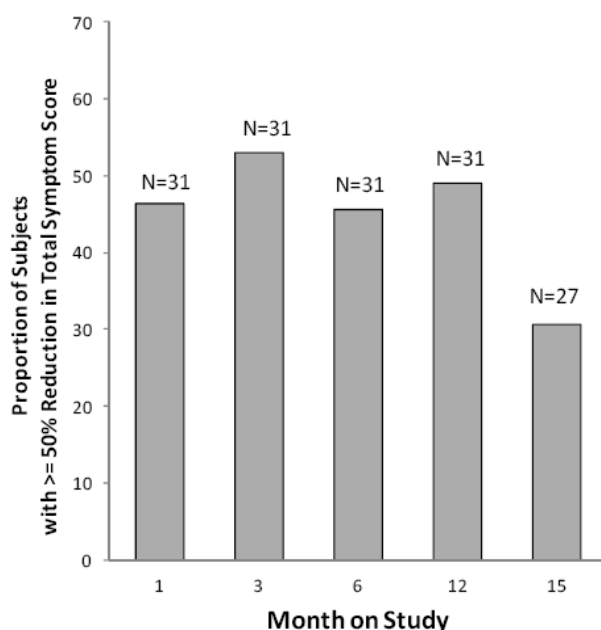
Treatment with INC424 is associated with a prompt decrease in spleen size that is durable over many months. Ad hoc subgroup analysis showed the proportion of responding patients in the pooled 15 mg BID and 25 mg BID groups (most effective regimens) to be similar among patients with or without the JAK2V617F mutation.

Disease progression of MPN is 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 BMI at Baseline in the lowest quartile (BMI below 22).

For the patients with available data, there was a prompt shift in the Eastern Cooperative Oncology Group (ECOG) performance scores in individuals with scores of 1 or 2 towards a score of 0, and this improvement was maintained over 96 weeks of therapy. The modified Myelofibrosis Symptom Assessment Form (MFSAF) developed by [Mesa et al. \(2007\)](#) and based on an international internet-based survey of over 1,000 patients with MPN, is being used to probe a range of constitutional symptoms that are related to splenomegaly (including impaired ability to move around and early satiety) and elevated cytokines (including fatigue, night sweats and pruritus). [Figure 1-2](#) illustrates the symptoms response for patients who initiated their individualized optimized regimens at a starting dose of 15 mg BID.



**Figure 1-2 Proportion of patients with at least 50% reduction in total symptom score in Study INCB018424-251 who began dosing at 15 mg BID**



In summary, INC424 is associated with prompt and marked reduction in spleen size, gains in total body weight, improvement in ECOG performance status scores and improvement in constitutional symptoms that can be debilitating in this patient population. At this time, studies demonstrate that the response to INC424 therapy is independent of *JAK2* V617F mutational status.

INC424 has been well tolerated by this aged population with advanced disease. Adverse events regardless of relationship to the drug occurring in at least 20% of the 154 patients included in the safety database through December 31, 2009 were restricted to anemia (48%, 74 patients), thrombocytopenia (45%, 70 patients), diarrhea (29%, 44 patients), and fatigue (23%, 36 patients). Most non-hematologic adverse events were mild to moderate in severity and considered unrelated to study drug administration. Both anemia and thrombocytopenia can be explained by JAK-inhibition, and are therefore not unexpected. Thrombocytopenia represents the DLT in the MF population. Patients initially assigned to the 50 mg BID dose group had an incidence of Grade 3 thrombocytopenia of 60% (3 of 5 patients) and of Grade 4 thrombocytopenia of 20% (1 of 5 patients). The 25 mg BID dose group, the largest dose group examined, had incidences of Grade 3 and 4 thrombocytopenia of 36% and 11% (12 and 5 of 47 patients), respectively. For the 25 mg BID dose group, patients exhibiting these Grade 3 or 4 declines in platelets had, in general, entered the study with platelet counts below 200,000/ $\mu$ L. In a subsequent cohort, patients were assigned to an initial dose of 15 mg BID provided their Baseline platelet count was  $>200,000/\mu$ L; the incidence of Grade 3 thrombocytopenia was markedly reduced (1 of 35 patients) and there were no Grade 4 events. For nearly all patients, thrombocytopenia was rapidly reversible and manageable with dose interruption and/or reduction. Anemia, though dose dependent, largely reflects the low hemoglobin status at Baseline in this disease population. Because of the advanced disease present in many of the participants in Study [INCB 18424-251], there are a number of SAEs



that have been reported that were assessed as unrelated to study drug. Of related SAEs reported in the study to date, the most frequent are those reflecting inhibition of bone marrow function(s) (i.e., thrombocytopenia) and activation of inflammatory cytokines when the inhibitory influence of INC424 is removed due to drug interruption or discontinuation. See the IB for complete details on INC424 clinical study findings.

Based on the promising results from Study [INCB 18424-251], 2 separate phase III studies are underway in US, Canada, and Australia (Study [INCB 18424-351]) and Europe (Study [CINC424A2352]). Study [INCB 18424-351] is a randomized, double-blind trial which compares INC424 to placebo. Study [CINC424A2352] is a randomized, open-label trial which compares INC424 to best available therapy as determined by the Investigator for each individual patient randomized to the control group. For these studies, the primary endpoint is the proportion of patients achieving  $\geq 35\%$  reduction in spleen volume at Week 24 (Study [INCB 18424-351]) or at Week 48 (Study [CINC424A2352]) compared to Baseline. At this time, the results of the initial analysis of Study [INCB 18424-351] are available. A total of 309 patients were enrolled in the study. In the primary endpoint assessment, the proportion of patients achieving  $\geq 35\%$  reduction in spleen volume from Baseline to Week 24 was 41.9% in patients randomized to INC424 versus 0.7% in those randomized to placebo ( $p < 0.0001$ ). A statistical significance was also observed in the key secondary endpoint, symptomatic improvement as measured by the modified MFSAF. The safety profile of INC424 appeared to be consistent with the previous studies.

## 2 Rationale

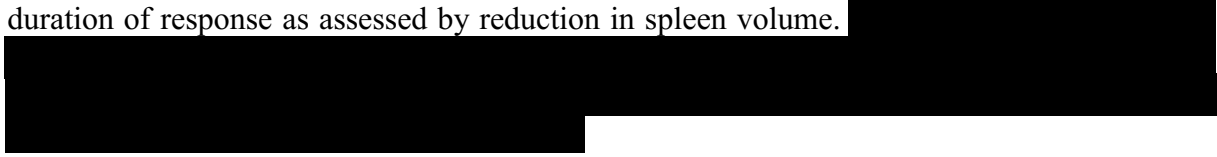
### 2.1 Study rationale and purpose

INC424 is a potent selective inhibitor of JAK1- and JAK2-STAT signaling pathways. These signaling pathways play a critical role in the pathogenesis of MPN, which forms the basis of development of INC424 for the treatment of MPN.

Current therapies for MF have limited efficacy, and most countries have no drugs approved for this indication. Most patients are managed initially with a wait-and-see approach, since the goal of treatment is palliative and not disease-modifying. However, certain drugs approved for other indications have been tried with limited success. The most commonly used drug is hydroxyurea, used primarily to control splenomegaly and elevated WBC and/or platelet counts. Other chemotherapy agents such as busulfan, 6-mercaptopurine, pipobroman, or thioguanine have been used. Immunomodulatory agents such as thalidomide, lenalidomide and interferon- $\alpha$  are sometimes employed. Agents aimed primarily at constitutional symptoms (such as prednisone), thrombocythemia (such as anagrelide), or even non-specific marrow-toxic agents (such as radiophosphorus or cladribine) have been tried. Splenectomy and splenic irradiation have been used to control spleen-related symptoms. No approach however is considered to be the standard of care, or is associated with sufficient disease control (Kroger et al. 2008).

The encouraging results from the phase I/II study in patients with MF support further studies in this patient population, and 2 phase III studies are underway in Western countries. However, no clinical trial has been conducted in Asian countries and a limited number of Asian patients have been enrolled on any study. An Asian multi-national phase II open-label study of

INC424 (Study [CINC424A2202]) in patients with PMF or post-PV/ET MF is therefore planned. The purpose of this study is to evaluate the efficacy and safety of INC424 in Asian MF patients. The primary objective is to determine the efficacy of INC424 as assessed by reduction in spleen volume at 24 weeks. The secondary objectives are to determine the safety and tolerability of INC424, to evaluate the effects of INC424 on patient reported outcomes as assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire score (EORTC QLQ-C30) and Seven-day modified MFSAF v2.0, and the duration of response as assessed by reduction in spleen volume.

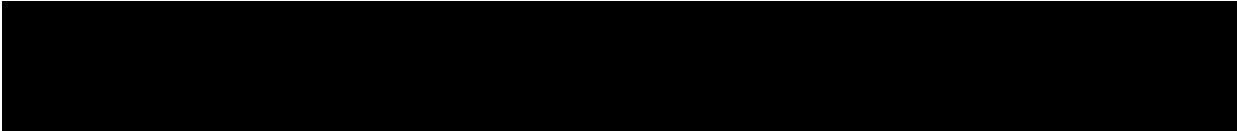


## 2.2 Rationale for the study design

This is a phase II open-label study evaluating the efficacy and safety of INC424 in MF patients with PMF or post-PV/ET MF. Patient population, dosing regimen, and assessments are basically in accordance with the phase III studies described above. The study will include only patients with poor prognosis who are at high risk or intermediate-2 risk according to the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria (Cervantes et al. 2009). The Screening and Baseline phases should not exceed 42 days combined. The length of these phases accommodates time required for discontinuation of all drugs used to treat MF at least 28 days prior to Baseline and the assessment of all inclusion and exclusion criteria and the Baseline assessment. The primary endpoint will be the proportion of patients achieving  $\geq 35\%$  reduction in spleen volume from Baseline to Week 24, which is based on an objective measure of spleen volume. Splenomegaly is a major source of morbidity and determinant of quality of life in MF patients (Mesa 2009). According to the IWG-MRT consensus panel a 50% reduction in palpable spleen length is considered clinically important (Tefferi et al. 2006). In Study [INCB 18424-251], a median decrease of  $\sim 35\%$  in spleen volume by MRI was observed with corresponding palpable spleen length in the same patients reduced by up  $\sim 50\%$ . Based on these data, a  $\geq 35\%$  reduction in spleen volume was selected as a clinically meaningful reduction as assessed by objective imaging. In accordance with the ongoing phase III studies and in order to obtain the most objective clinical data, magnetic resonance imaging (MRI) has been chosen as the primary modality of spleen volume measurement, and the spleen volume will be calculated by independent imaging. Patients who are not candidates for MRI will be evaluated with sequential computed tomography (CT). The primary endpoint will be assessed after 24 weeks of therapy. A safety Follow-up Visit will be held 30 (+10) days following the last dose of study drug in order to effectively evaluate post-treatment safety and tolerability. Patients who are benefiting from study drug will continue study treatment until they have access to treatment through commercial supplies, if applicable by local regulations.

## 2.3 Rationale for dose and regimen selection

INC424 is self-administered orally. In the phase I/II study in MF patients, Study [INCB 18424-251], twice daily dose regimens from 10 mg BID to 50 mg BID were examined. Based on the ongoing efficacy and safety data, there appears to be some individual variability in terms of sensitivity to thrombocytopenia and also clinical response, such that an optimal dose



for a given individual is likely to be between 10 mg BID and 25 mg BID, and that some opportunity for individual titration of dose within this range might offer the best balance of safety and efficacy for any individual patient. Therefore, patients enrolled in Study [INCB 18424-251] since August 2008 have initiated therapy at 15 mg BID, unless platelet count at Baseline was  $<200,000/\mu\text{L}$ , in which case initial dosing was at 10 mg BID. For these patients, the study protocol dictates a mandatory dose increase of 5 mg BID at Week 4 (to doses of 20 mg BID or 15 mg BID, respectively) for inadequate efficacy and adequate platelet count and ANC levels. A second, optional dose increase may occur at Week 8.

Table 2-1 shows the preliminary efficacy data based on the initial dose and average dose in Study [INCB 18424-251]. In this study, the majority of subjects were titrated to the most appropriate dosage; therefore, it is of interest to assess efficacy based on the average dose received. In general, a dose response was seen based on the average dose received with higher median percent reduction from Baseline in spleen length seen with higher doses.

**Table 2-1** Baseline and percent change from Baseline in spleen length at week 24 by initial and average dose in Study INCB 18424-251

Statistic	$\leq 10$ mg BID	$>10\text{--}\leq 15$ mg BID	$>15\text{--}\leq 20$ mg BID	$>20\text{--}\leq 25$ mg BID	$>25$ mg BID
Baseline, cm					
n	27	32		34	4
Mean (SD)	19.81 (7.4)	18.50 (5.6)		20.32 (6.1)	16.25 (8.0)
Median	19.00	17.50		20.00	19.00
Percent change from Baseline at Week 24 based on initial treatment					
n	18	28		32	3
Mean (SD)	-50.9 (32.3)	-54.4 (30.6)		-54.1 (35.4)	-65.7 (51.7)
Median	-50.802	-53.5		-54.087	-90.909
Percent change from Baseline at Week 24 based on average treatment					
n	21	27	14	17	2
Mean (SD)	-47.4 (32.1)	-41.9 (34.1)	-61.5 (29.9)	-69.9 (27.3)	-95.5 (6.4)
Median	-47.058	-42.105	-60.833	-76	-95.454

Table 2-2 presents a summary of treatment-related adverse events occurring in  $\geq 5\%$  of subjects in all initial treatment groups in Study [INCB 18424-251]. Treatment-related AEs that occurred in  $\geq 5\%$  of subjects were restricted to thrombocytopenia, anemia, weight increase, diarrhea, and fatigue. Although anemia was the most frequently reported AE, overall, thrombocytopenia was the most frequently reported treatment-related AE.

**Table 2-2** Summary of treatment-related adverse events reported in at least greater or equal 5 % of subjects in Study INCB 18424-251

	10 mg BID	15 mg BID	25 mg BID
Preferred Term, n (%)	(N=30)	(N=35)	(N=47)
Any event	21 (70.0)	22 (62.9)	41 (87.2)
Thrombocytopenia	12 (40.0)	8 (22.9)	29 (61.7)
Anemia	5 (16.7)	6 (17.1)	22 (46.8)
Weight increased	2 (6.7)	0	3 (6.4)
Diarrhea	0	6 (17.1)	4 (8.5)
Fatigue	3 (10.0)	3 (8.6)	2 (4.3)

Thrombocytopenia represents the DLT for INC424 in the MF population. Table 2-3 presents a summary of the maximum Grade 3 or 4 events of thrombocytopenia by initial treatment group. Thrombocytopenia occurred more often in patients with a Baseline platelet count of less than  $200 \times 10^9$  per liter. Notably, the incidence of thrombocytopenia to date at 15 mg BID, including those patients with subsequent dose escalations to 20 mg BID and 25 mg BID, is similar to that of the 10 mg BID dose group. Also, thrombocytopenia showed increasing frequency at doses of 25 mg BID.

**Table 2-3** Summary of maximum grade greater or equal 3 post-baseline thrombocytopenia events by initial treatment group in Study INCB 18424-251

	10 mg BID	15 mg BID	25 mg BID
	(N=30)	(N=35)	(N=47)
Maximum post-Baseline thrombocytopenia, n (%)			
Grade 3	6 (20.0)	1 (2.9)	12 (25.5)
Grade 4	0	0	5 (10.6)

Based on these data, in Study [CINC424A2202] as well as ongoing western phase 3 studies (Study [INCB-18424-351] and [CINC424A2352]), 15 mg BID will be the starting dose for all patients entering the study with a platelet count between 100,000/ $\mu$ L and 200,000/ $\mu$ L (inclusive), whereas 20 mg BID will be the starting dose for all patients entering the study with a platelet count  $>200,000/\mu$ L. With this dosing scheme, patients with higher platelet counts will start at a dose more likely to result in robust spleen reduction, while patients with a lower platelet level will begin with a dose that appears to have a very low incidence of thrombocytopenia. An optional dose increase of 5 mg BID for inadequate efficacy will occur at Week 4, provided platelet counts and ANC levels are in a satisfactory range. Mandatory dose decreases for safety reasons will be dictated by platelet count and ANC levels. These dose increases and decreases are summarized in Section 6.2.

The pharmacokinetics of INC424 in Japanese healthy volunteers (preliminary results of Study [CINC424A1101]) was similar to those in healthy volunteers studied in Western trials ([INCB 18424-131], [INCB 18424-132], [INCB 18424-138]). This is consistent with the fact that the primary metabolic enzyme of INC424 is CYP3A4 and ethnic differences are not expected in this enzyme expression or activity. These results suggest that the pharmacokinetics in an Asian population will be similar to the western population.

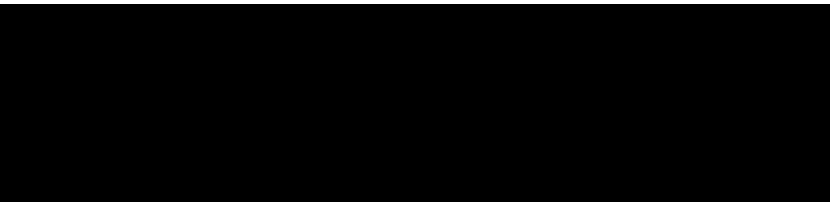
### 3 Objectives and endpoints

#### Primary Objective

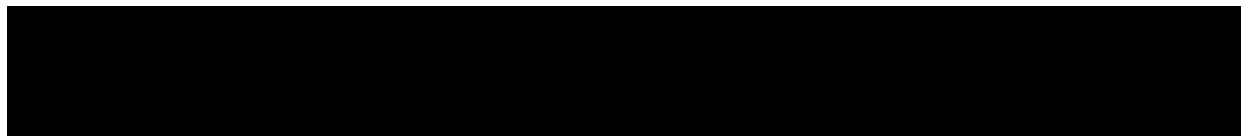
- To determine the efficacy of INC424 as assessed by reduction in spleen volume

#### Secondary Objectives

- To determine the safety and tolerability of INC424
- To evaluate the effects of INC424 on patient reported outcomes
- To evaluate the duration of response as assessed by reduction in spleen volume

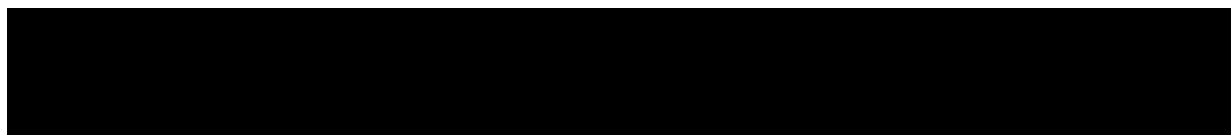
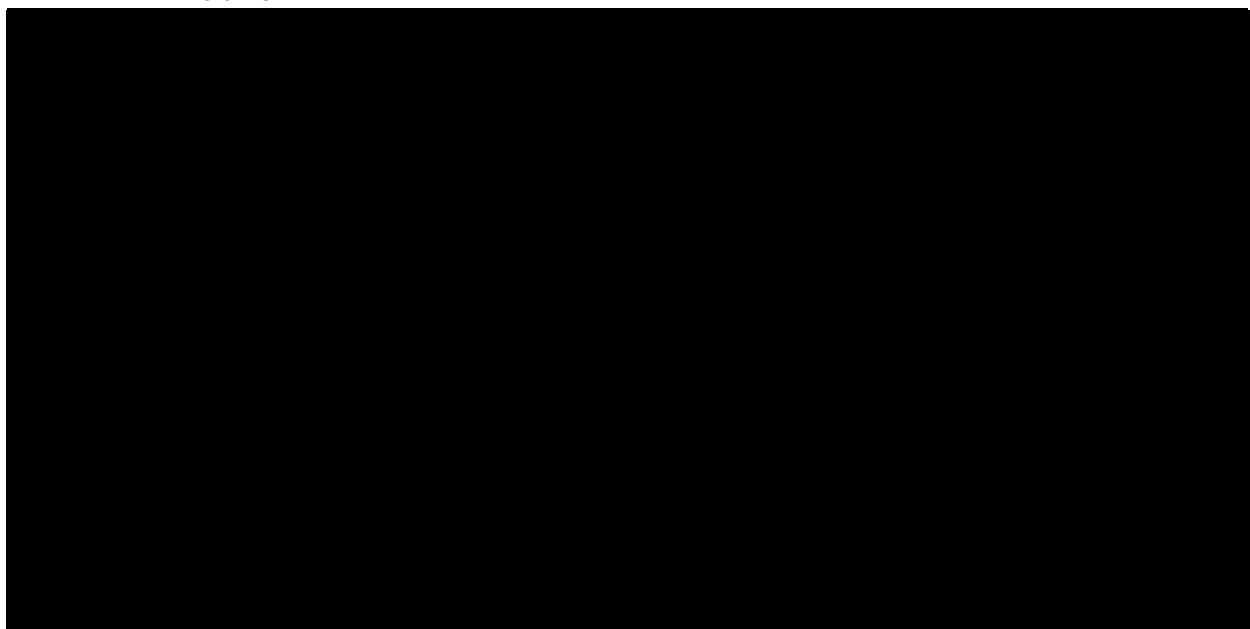


Objectives and related endpoints are described in [Table 3-1](#) below.



**Table 3-1 Objectives and related endpoints**

	Objective	Endpoint	Analysis
Primary	To determine the efficacy of INC424 as assessed by reduction in spleen volume	<ul style="list-style-type: none"> <li>Proportion of patients achieving <math>\geq 35\%</math> reduction in spleen volume from Baseline to Week 24 as measured by MRI (or CT scan in applicable patients)</li> </ul>	Refer to <a href="#">Section 10.4</a>
Secondary	To determine the safety and tolerability of INC424	<ul style="list-style-type: none"> <li>Safety and tolerability will be assessed by monitoring the frequency, duration and severity of adverse events, performing physical exams, and evaluating changes in vital signs, electrocardiograms (ECGs), serum chemistry, hematology and urinalysis results. Toxicity will be assessed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03.</li> </ul>	Refer to <a href="#">Section 10.5.5</a>
Secondary	To evaluate the effects of INC424 on patient reported outcomes	<ul style="list-style-type: none"> <li>Change in EORTC QLQ-C30 score from Baseline to Week 24</li> <li>Change in total symptom score from Baseline to Week 24, as assessed by Seven-day modified MFSAF v2.0</li> </ul>	Refer to <a href="#">Sections 10.5.1</a> and <a href="#">10.5.2</a>
Secondary	To evaluate the duration of response as assessed by reduction in spleen volume	<ul style="list-style-type: none"> <li>Best response rate</li> <li>Duration of maintenance of a <math>\geq 35\%</math> reduction from Baseline in spleen volume</li> </ul>	Refer to <a href="#">Sections 10.5.3</a> and <a href="#">10.5.4</a>



## 4 Study design

### 4.1 Description of study design

This is an Asian multi-national phase II open-label study evaluating the efficacy and safety of INC424 in patients with PMF or post-PV/ET MF who have splenomegaly of at least 5 cm below the costal margin by manual palpation, and 2 or more risk factors (intermediate-2 or high risk) defined by the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) ([Cervantes et al. 2009](#)). The study will be conducted in four Asian countries, i.e., China, Japan, Korea and Taiwan. The target number of patients for this study is 110 in total (see [Section 10.8](#)).

The study is composed of 4 phases.

#### Screening Phase

Screening evaluations will be performed to determine the eligibility for the study, and should be conducted between Day -42 and Day -8.

#### Baseline Phase

Baseline evaluations will be performed in patients who have signed the Informed Consent Form (ICF) and meet all the eligibility criteria in the Screening phase. Procedures for the Baseline Visit will be conducted between Day -7 and Day -1. The Baseline MRI scan will be conducted between Day -28 and Day -7 to allow ample time for the central reader to verify image quality prior to the initial administration of study drug. Bone marrow aspiration and biopsy will be conducted between Day -42 and Day -1.

#### Treatment Phase

After the Screening and Baseline phases, patients who meet all the eligibility criteria will be able to start treatment with INC424. The starting dose of INC424 will be determined based on Baseline platelet count; patients with Baseline platelet count of 100,000/ $\mu$ L to 200,000/ $\mu$ L will begin dosing at 15 mg BID, and those with Baseline platelet count higher than 200,000/ $\mu$ L will begin dosing at 20 mg BID. A standardized dosing paradigm will be used to determine dose adjustments for safety and efficacy so that each patient is titrated to their most appropriate dose (see [Section 6.2](#)).

In order not to withhold INC424 from patients who are benefiting from the treatment, INC424 will be made available until the patients have access to treatment through commercial supplies (if applicable by local regulations) or the patients are permanently discontinued from the study, whichever comes first.

#### Follow-up

A safety Follow-up Visit will be conducted 30 (+10) days following the last dose of study drug was received.



## 4.2 Timing of interim analyses

A single interim analysis is planned when the first 50 patients have completed Week 24 Visit or have discontinued from the study prior to Week 24. The primary aim of the interim analysis is to assess the efficacy and safety of INC424 in Asian MF patients and to achieve an earlier regulatory filing to health authorities with the interim efficacy and safety data. If this interim analysis shows at least the pre-specified number of responders (see [Section 10.7](#)), the Steering Committee (SC) will discuss the safety and efficacy results, and will make a final decision on the applicability of a submission. Irrespective of this decision, the study will move to the second stage in order to enroll additional patients so that the primary analysis will be performed with approximately 110 patients in total. The alpha for the final analysis will be adapted to alpha spent at the interim analysis (see [Section 10.7](#)).

## 4.3 Definition of end of the study

The end of the study (last patient last visit) will occur after all patients in the study have completed their last assessment as per protocol. Patients who are benefiting from study drug will continue study treatment unless one or more withdrawal criteria ([Section 7.1.4.1](#)) are met and if the treatment with INC424 is considered the patient's best therapeutic option by the Investigator. The study treatment will continue until the patients have access to study drug through commercial supplies, if applicable by local regulations. The last assessment for each patient is the Follow-up Visit that occurs 30 days after the last dose of study drug.

## 4.4 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and the same assessments should be performed as described in [Section 7.1.4.1](#) for a withdrawn patient. The Investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The Investigator will be responsible for informing Institutional Review Board (IRB) and/or Independent Ethics Committee (IEC) of the early termination of the trial.

# 5 Population

## 5.1 Patient population

Male or female individuals 18 years of age or older will be eligible if they have been diagnosed with PMF or post-PV/ET MF, have a palpable spleen measuring 5 cm or greater below the costal margin, and have 2 or more risk factors as defined by IWG-MRT ([Cervantes et al. 2009](#)). Patients are allowed to have received prior therapy for MF. Patients who are receiving therapy for MF must discontinue all drugs used to treat MF at least 28 days prior to Baseline.

The Screening phase is defined as the period beginning on the day that written Informed Consent is given. The Screening plus Baseline phases cannot exceed 42 consecutive days prior to the first dose of study drug. Patients enrolled in the study cannot participate in any concurrent clinical study of other investigational agents or devices, or receive any other



therapies for MF during the study. Patients who have completed or discontinued the study may not be re-enrolled in the study for a second course of treatment.

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

A written ICF must be obtained according to the local guidelines before the start of any Screening procedures.

## 5.2 Inclusion criteria

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

1. Patients 18 years of age or older
2. Patients must have been diagnosed with PMF or post-PV/ET MF, irrespective of the JAK2 mutation status. The diagnosis should be made in the best determination of the Investigator based upon the 2008 World Health Organization (WHO) criteria ([Thiele et al. 2008](#)) for PMF, and upon the IWG-MRT criteria ([Barosi et al. 2008](#)) for post-PV/ET MF
3. Patients must have a palpable spleen measuring 5 cm or greater from the costal margin to the point of greatest splenic protrusion
4. Patients must have 2 or more risk factors (intermediate-2 or high risk) as defined by IWG-MRT ([Cervantes et al. 2009](#)). The risk factors are:
  - Age >65 years
  - Presence of constitutional symptoms (weight loss, fever, night sweats)
  - Marked anemia (Hgb <10 g/dL)\* or packed red blood cell transfusion-requiring
  - Leukocytosis (history of WBC >25,000/ $\mu$ L)
  - Circulating blasts  $\geq 1\%$

\*Hgb <10 g/dL must be demonstrated during the Screening Visit for patients who are not transfusion dependent. Patients receiving regular transfusions of packed red blood cells will be considered to have Hgb <10 g/dL for the purpose of evaluation of risk factors.

5. Patients with circulating blast count of <10%
6. Patients with an ECOG performance status of 0-2
7. Patients with adequate bone marrow reserve as follows:
  - Absolute neutrophil count (ANC)  $\geq 1,000/\mu$ L and
  - Platelet count  $\geq 100,000/\mu$ L without the assistance of growth factors, thrombopoietic factors or platelet transfusions
8. Patients must not currently have the option of stem cell transplantation, either because they are not a candidate, or because a suitable donor is not available
9. Patients must have discontinued all drugs used to treat underlying MF no later than 28 days prior to the first Baseline assessment (except for the MRI scan and bone marrow examinations)
10. Patients who have not previously received treatment with a JAK inhibitor

### 5.3 Exclusion criteria

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

1. Patients with impaired liver or renal function as demonstrated by:
  - Direct bilirubin  $\geq 2$  x upper limit of laboratory normal (ULN)
  - Alanine aminotransferase (ALT)  $> 2.5$  x ULN
  - Creatinine  $> 2.0$  mg/dL
2. Patients with clinically significant bacterial, fungal, mycobacterial, parasitic or viral infection (Patients with acute bacterial infections requiring antibiotic use should delay Screening/enrollment until the course of antibiotic therapy has been completed)
3. Patients with active hepatitis A, B, C, or HIV-positivity at Screening, defined as positivity for IgM-HA Ab test, HBs Ag test, HCV Ab test or HIV Ab test. Patients who are negative for HBs Ag test but positive for either HBs Ab test or HBc Ab test will be excluded if HBV-DNA test is positive
4. Patient must not have any concomitant malignancies and must be fully recovered from treatment for any other malignancy with no evidence of persistent disease
5. Patients with any history of significant congenital or acquired bleeding disorder
6. Patients with any history of platelet counts  $< 50,000/\mu\text{L}$  or ANC  $< 500/\mu\text{L}$  except during treatment for MPN or treatment with cytotoxic therapy for any other reason
7. Patients who have had splenic irradiation within 12 months prior to Screening
8. Patients undergoing treatment with hematopoietic growth factor receptor agonists (i.e., erythropoietin, granulocyte colony stimulating factor, romiplostim, eltrombopag) at any time within 14 days prior to Screening or 28 days prior to Baseline
9. Patients under ongoing treatment with another investigational medication not intended for MF or having been treated with such an investigational medication within 14 days prior to Baseline or within 6-half lives of the investigational product, whichever is longer
10. Patients with a history of myocardial infarction or acute coronary syndrome within 6 months prior to Screening
11. Patients with currently uncontrolled or unstable angina
12. Patients with currently rapid or paroxysmal atrial fibrillation
13. Resting heart rate  $> 110$  beats per minute
14. Resting systolic blood pressure  $> 160$  mm Hg
15. Resting diastolic blood pressure  $> 100$  mm Hg
16. Patients who are unable to comprehend or are unwilling to sign the ICF
17. Patients with active alcohol or drug addiction that would interfere with their ability to comply with the study requirements
18. Females who are pregnant or currently breastfeeding
19. Patients of childbearing potential who are unwilling to take appropriate precautions (from Screening through Follow-up) to avoid fathering a child or becoming pregnant
  - Females are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical

profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least 6 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.

- For females of childbearing potential, appropriate precautions should be “highly effective” in preventing the occurrence of pregnancy ([Appendix III](#)). These methods should be communicated to the patients and their understanding confirmed
- For males, condom during dosing and for 5 times the terminal  $t_{1/2}$  (about 15 hours) is required.

20. Patients with any concurrent condition that, in the Investigator’s opinion, would jeopardize the safety of the patient or compliance with the protocol

## 6 Treatment

### 6.1 Investigational treatment, supportive treatment

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

INC424 tablets will be administered orally, without regard to food, in an outpatient setting in accordance with specified dosing schedules.

On all other days corresponding to study visits, patients will take the morning dose of study drugs prior to the visit.

#### 6.1.1 Dosing regimen

The dosage strength is 5 mg/tablet INC424 phosphate (free base equivalent).

The starting dose of INC424 tablets will be determined based on Baseline platelet count as shown in [Table 6-1](#).

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

Study treatment	Pharmaceutical form and route of administration	Dose	Frequency
INC424	Tablet for oral use	Starting dose 15 mg BID for patients with Baseline platelet count of 100,000/ $\mu$ L to 200,000/ $\mu$ L (inclusive) or 20 mg BID for those with Baseline platelet count >200,000/ $\mu$ L (approximately 12 hours apart : morning and night), to be increased or decreased per standardized dosing paradigm (see <a href="#">Section 6.2</a> )	Twice daily, unless instructed

A standardized dosing paradigm will be used to determine dose adjustments for safety and efficacy so that each patient is titrated to their most appropriate dose (see [Section 6.2](#)). Doses

will not exceed 25 mg BID and will not be less than 5 mg BID (or 5 mg QD if used with a concomitant strong CYP3A4 inhibitor).

### **6.1.2 Treatment duration**

Patients who are benefiting from study drug will continue study treatment unless one or more withdrawal criteria ([Section 7.1.4.1](#)) are met and if the treatment with INC424 is considered the patient's best therapeutic option by the Investigator. The study treatment will continue until the patients have access to study drug through commercial supplies, if applicable by local regulations.

## **6.2 Dose modification**

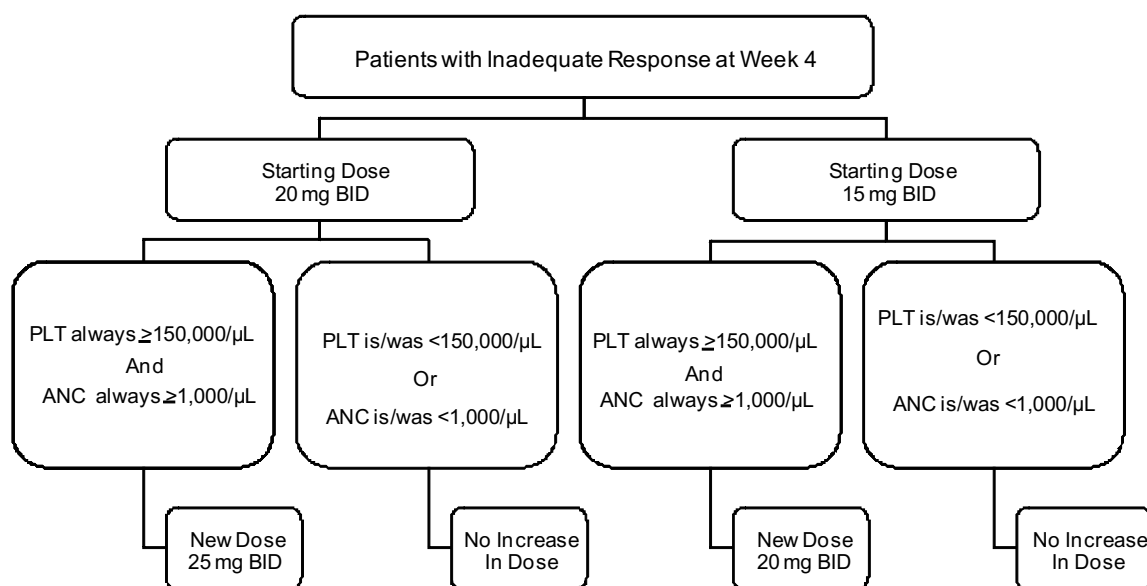
### **6.2.1 Dose increase for inadequate efficacy**

#### **6.2.1.1 Dose increase at Week 4**

As indicated in [Section 6.1.1](#), the initial dose of INC424, will be determined by the Baseline platelet count. [Figure 6-1](#) shows dose increase strategies because of inadequate efficacy at Week 4. At Week 4, dose increase of INC424 is allowed for patients who show inadequate efficacy as demonstrated by palpable spleen length below the costal margin that has been reduced by <40% at the Week 4 Visit relative to Baseline, if all of the following conditions are met:

- The patient must have had a platelet count  $\geq 150,000/\mu\text{L}$  at every assessment since Baseline
- The patient must have had ANC  $\geq 1,000/\mu\text{L}$  at every assessment since Baseline

**Figure 6-1 Strategies for dose increase because of inadequate efficacy at Week 4**



PLT = Platelet count, ANC = Absolute neutrophil count

#### 6.2.1.2 Dose increase beyond Week 4

After Week 4, dose increase of INC424 is allowed for patients who show an increase in spleen length by manual palpation by 2 cm or greater compared to the on-study nadir (lowest palpable spleen measurement during the study, including Baseline), if all of the following conditions are met:

- The dose increase may only occur in the 4-week period following the study visit at which a regularly scheduled MRI occurs (i.e., the 4 weeks following Week 12, 24, 36, etc)
- The MRI for that study visit must have been performed
- The platelet count and ANC levels for that visit must be available
- The patient must not have had a prior safety-related dose reduction
- The patient must have had a platelet count  $\geq 150,000/\mu\text{L}$  at every assessment since Baseline
- The patient must have had ANC  $\geq 1,000/\mu\text{L}$  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 both 2 and 4 weeks after the dose increase by an Extra Visit. The Extra Visit may be skipped if it takes place within 7 days of any other study visit.

Dose adjustment for safety, and reinstitution of doses as described in [Section 6.2.2](#) will apply whether the patient is on the original dose, or a dose that was increased for lack of efficacy.

## 6.2.2 Dose modification for safety

### 6.2.2.1 Interruption or dose reduction

For all patients, there are mandatory dose decreases or interruptions for hematologic and non-hematologic safety that might be observed while on INC424 therapy. In addition to mandatory dose interruption or decrease, there are mandatory criteria for permanent discontinuation of INC424 (see [Section 7.1.4.1](#)).

For hematologic safety, dosing must be held if platelet counts decline below 50,000/ $\mu$ L, or if ANC falls below 500/ $\mu$ L while receiving INC424. Doses must be decreased for platelet count values <125,000/ $\mu$ L as shown in Table 6-2 with optional restarting or resuming prior dose after recovery (see [Section 6.2.2.2](#)). 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/ $\mu$ L or ANC <1,000/ $\mu$ L and at least two times weekly for platelet count <50,000/ $\mu$ L or ANC <500/ $\mu$ L. The dose reduction strategy in Table 6-2 covers the starting doses (15 mg BID and 20 mg BID), possible doses after an increase for inadequate efficacy (20 mg BID and 25 mg BID), and doses that might be present after a prior dose reduction (down to 5 mg BID).

**Table 6-2 Dose reduction of INC424 for safety in patients with platelet count declines**

Platelet Count at Time of Decline (in thousands)	▼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 ▼				
$\geq 125$ K/ $\mu$ L	No dose reduction required				
100 to <125 K/ $\mu$ L	20 mg BID	20 mg BID	15 mg BID	10 mg BID	5 mg BID
75 to <100 K/ $\mu$ L	10 mg BID	10 mg BID	10 mg BID	10 mg BID	5 mg BID
50 to <75 K/ $\mu$ L	5 mg BID	5 mg BID	5 mg BID	5 mg BID	5 mg BID
<50 K/ $\mu$ L	MUST HOLD DOSING				

Severe anemia may be managed by transfusion therapy as necessary. If hemoglobin cannot be maintained  $\geq 6.5$  g/dL despite the use of transfusion therapy, study treatment must be discontinued (see [Section 6.2.4](#)).

For non-hematologic safety, dosing must be held if a Grade 3 or greater study drug-related non-hematologic toxicity occurs.

Patients whose treatment is interrupted due to an adverse event or abnormal laboratory value must be followed at least once a week for 4 weeks, and subsequently at 4-week intervals, until resolution or stabilization of the event, whichever comes first. If a patient requires a dose delay of  $\geq 8$  weeks because of hematologic or non-hematologic toxicities, then the patient must be discontinued from the study.

Additionally, in a patient who develops hepatic impairment or end-stage renal failure requiring dialysis during the study, a caution should be exercised in administering study drug as the patient may receive higher drug exposure. For a patient with hepatic impairment, as a general guidance, it is recommended that the dose be reduced by 50%, then the patient be

carefully monitored and the dose titrated accordingly. For a patient with end-stage renal failure requiring dialysis, it is recommended that the Investigator consult with the Sponsor for further advice.

### 6.2.2.2 Restarting or resuming previous dose

Dosing may be restarted or increased following recovery of platelet counts and/or ANC to acceptable levels as illustrated in Table 6-3, provided platelets counts are  $\geq 50,000/\mu\text{L}$  and ANC levels are  $\geq 500/\mu\text{L}$ . 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 selected.

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  $<500/\mu\text{L}$  necessitate immediate dose interruption. ANC level recovery to above  $500/\mu\text{L}$  but less than  $750/\mu\text{L}$  will allow dosing to be restarted at 5 mg BID, and ANC levels above  $750/\mu\text{L}$  but  $<1000/\mu\text{L}$  may restart at 10 mg BID. ANC level increases to above  $1,000/\mu\text{L}$  will allow a further dose increase to a maximum of 20 mg BID.

After restarting using the guidelines in Table 6-3, if it is found that a patient cannot tolerate the lowest allowed dose (5 mg BID, or 5 mg QD if used with a concomitant strong CYP3A4 inhibitor, see [Section 6.2.3](#)) due to platelets falling below  $50,000/\mu\text{L}$ , neutrophils falling below  $500/\mu\text{L}$ , or hemoglobin falling below 6.5 g/dL despite the use of packed red blood cell transfusion therapy to treat anemia, drug must be permanently discontinued ([Section 6.2.4](#)).

**Table 6-3 Restarting or increasing INC424 dose after safety interruption or dose reduction for hematologic safety**

Current Platelet Count (in thousands)	▼ Dose Restart or Dose Increase Guidelines ▼
$<50 \text{ K}/\mu\text{L}$	Continue hold
50 to $<75 \text{ K}/\mu\text{L}$	5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID
75 to $<100 \text{ K}/\mu\text{L}$	10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID
100 to $<125 \text{ K}/\mu\text{L}$	15 mg BID
$\geq 125 \text{ K}/\mu\text{L}$	20 mg BID
Current ANC Level	▼ Dose Restart or Dose Increase Guidelines ▼
$<500/\mu\text{L}$	Continue hold
500 to $<750/\mu\text{L}$	5 mg BID for at least 2 weeks; if stable, may increase to 10 mg BID
750 to $<1,000/\mu\text{L}$	10 mg BID for at least 2 weeks; if stable, may increase to 15 mg BID
1,000 to $<1,500/\mu\text{L}$	15 mg BID for at least 2 weeks; if stable may increase to 20 mg BID
$\geq 1,500/\mu\text{L}$	20 mg BID

All non-hematologic toxicities that have a study drug-related causality should be resolved to no higher than Grade 1 before dosing resumes. It is recommended that the Investigator consult with the Sponsor before restarting or increasing dosing following recovery of non-hematologic toxicities.

Patients whose treatment is interrupted due to splenectomy may be allowed to restart dosing, if fully recovering from the surgery within 12 weeks of the dosing interruption.

### **6.2.3 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 isozyme. With concomitant dosing of strong CYP inhibitors such as oral ketoconazole, plasma exposure of INC424 increases approximately 2-fold. Thus, a dose reduction of up to 50% for INC424 is appropriate for patients who take ketoconazole or other strong CYP3A4 inhibitors as concomitant medication. BID doses will be decreased to the corresponding QD doses 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

Strong inhibitors of CYP3A4 include oral ketoconazole, clarithromycin, itraconazole, nefazodone, telithromycin ([Flockhart 2007, Appendix V](#)). Based on the very low overall bioavailability of topical ketoconazole, no dosage adjustment is needed for use with topical ketoconazole.

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.

### **6.2.4 Treatment discontinuation**

If 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 (see [Section 6.2.2](#)). Although study guidelines provide for dose reduction/interruption, the following guidelines should be used to determine whether permanent discontinuation of study drug is necessary.

#### **6.2.4.1 Discontinuation criteria for disease progression**

The following events are considered disease progression.

- A  $\geq 25\%$  increase in spleen volume by MRI compared to Baseline: the Investigator will be notified via the central reader
- Splenic irradiation
- Leukemic transformation as defined by a bone marrow or a peripheral blood blast count of  $\geq 20\%$
- Splenectomy



In the event that a patient experiences leukemic transformation, requires therapy with splenic irradiation, or experiences a  $\geq 25\%$  increase in spleen volume by MRI compared to Baseline, study drug must be permanently discontinued. If a patient undergoes splenectomy, and the Investigator believes that it is in the patient's benefit to continue therapy with INC424 due to symptomatic improvement, the patient may continue therapy assuming s/he has fully recovered from the splenectomy procedure within 12 weeks.

#### **6.2.4.2 Discontinuation criteria for adverse events**

For hematologic safety, study drug must be permanently discontinued if the lowest allowed dose (5 mg BID, or 5 mg QD if used with a concomitant strong CYP3A4 inhibitor) is not tolerated due to the following:

- Platelets cannot be maintained  $\geq 50,000/\mu\text{L}$
- ANC cannot be maintained  $\geq 500/\mu\text{L}$
- Hemoglobin cannot be maintained  $\geq 6.5$  g/dL despite the use of transfusion therapy (or if the patient will not accept blood transfusions)

For non-hematologic safety, study drug must be permanently discontinued if the lowest allowed dose (5 mg BID, or 5 mg QD if used with a concomitant strong CYP3A4 inhibitor) is not tolerated due to the following:

- The occurrence of a Grade 4 laboratory abnormality that is considered related to study drug, and is clinically significant in the view of the Investigator. Exceptions not requiring study withdrawal include but are not limited to serum iron, total bilirubin not accompanied by direct bilirubin of  $2 \times \text{ULN}$ , triglycerides, total cholesterol, HDL cholesterol, or abnormalities in urinalysis 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 study drug. Exceptions not requiring study withdrawal include but are not limited to 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 discretion of the Investigator.

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

### **6.3 Concomitant medications**

#### **6.3.1 Permitted concomitant therapy**

Patient must be told to notify the study site about any new medications he/she takes after the start of study drug. All concomitant medications and treatments must be recorded in the eCRF. Any prior medication received up to 28 days prior to the first dose of study drug will be

recorded in the eCRF. All prior medications used to treat MF disease will be recorded. All concomitant treatments during the trial will also be recorded in the eCRF.

### 6.3.2 Restricted/allowed therapies

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

- Systemic corticosteroid doses greater than the equivalent of 10 mg prednisolone per day are prohibited, unless use is part of an INC424 dose tapering strategy (see Section 6.3.4)
- In patients for whom warfarin or heparin use will be initiated, the degree of thrombocytopenia should be considered, coagulation parameters monitored and dose of anti-coagulant adjusted accordingly
- Hematopoietic growth factor receptor agonists (i.e., erythropoietin, granulocyte colony stimulating factor, romiplostim, eltrombopag) are not recommended. INC424 may interfere with efficacy, and they may cause an increase in spleen size
- Low dose aspirin ( $\leq 150$  mg/day) and non steroidal anti-inflammatory agents (acetaminophen, ibuprofen) may be used. Aspirin in doses exceeding 150 mg per day is prohibited
- Inducers or inhibitors of the metabolizing enzyme CYP3A4 ([Flockhart 2007](#), [Appendix V](#)):
  - When concomitant administration of a strong inhibitor of CYP3A4 is required for patient management, the dose of INC424 tablets must be adjusted (see [Section 6.2.3](#)).
  - The use of strong CYP3A inducers is prohibited (Section 6.3.3)
  - The use of mild-to-moderate inhibitors or inducers of CYP3A4 ([Appendix V](#)) is discouraged; alternative therapies should be considered wherever possible. Should one of these medications be medically necessary, its use should be documented; however dose adjustment of INC424 is not required

### 6.3.3 Prohibited therapies

The following medications are prohibited during the study:

- Any investigational medication other than INC424. Use of such medications within 14 days or 6 half-lives, whichever is longer, prior to the Baseline and during the study through the Follow-up Visit is prohibited
- Use of any other drugs for MF including hydroxyurea, interferon, thalidomide, busulfan, lenalidomide or anagrelide is not permitted within 28 days prior to Baseline and at any time during participation in the study
- Potent inducers of CYP3A4 (rifampin and St. John's Wort) are not permitted

### 6.3.4 Optional dose tapering strategy in the event of drug discontinuation

When a decision is made to permanently discontinue INC424 for reasons other than low platelet counts, ANC levels, or hemoglobin, 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 study drug dosage over 1-2 weeks or use of other medications to manage clinical signs and/or symptoms caused by 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 in anticipation of the possibility of occurrence of withdrawal symptoms. 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 (see [Section 6.2.4](#)).

## **6.4 Patient numbering**

Each patient is identified in the study by a Patient number with a length of 9 digits, which is a combination of his/her Site ID and subject number (the last 5 digit of the Patient number) when the patient is first enrolled. The Site ID is assigned by the Sponsor to the Investigative site. Upon signing the ICF, the subject number is assigned by the Investigator. At each site, the first patient is assigned subject number 1, and subsequent patients are assigned consecutive numbers (i.e., the second patient is assigned subject number 2, the third patient is assigned subject number 3).

After the confirmation of the inclusion and exclusion criteria, the Investigator will send an enrollment form (if patient is eligible) to the Sponsor by fax or e-mail. The Sponsor will then notify the registration confirmation to the study site. The Investigator or designee will notify the initiation of treatment in each patient to the Sponsor by fax or e-mail. The starting dose of study drug will be determined by the Investigator, based on Baseline platelet count (see [Section 6.1.1](#)).

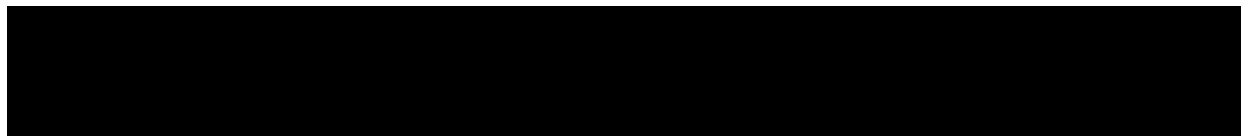
If the patient fails to be started on treatment for any reason, the reason will be entered into the Screening log eCRF. The Sponsor must be notified within 7 days that the patient was not started on treatment.

## **6.5 Study drug supply**

### **6.5.1 Study drug preparation and dispensation**

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

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



**Table 6-4 Preparation and dispensing**

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

### 6.5.2 Study drug packaging and labeling

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

**Table 6-5 Packaging and labeling**

Study drugs	Packaging	Labeling (and dosing frequency)
INC424	Tablets in bottle	INC424 5 mg

### 6.5.3 Drug supply and storage

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

**Table 6-6 Supply and storage**

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

### 6.5.4 Drug compliance and accountability

#### 6.5.4.1 Drug compliance

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

#### 6.5.4.2 Drug accountability

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

At study close-out, and, as appropriate during the course of the study, the Investigator will return all used and unused study drug, packaging, drug labels, and a copy of the completed

drug accountability ledger to the Sponsor monitor or to the Sponsor address provided in the Investigator folder at each site.

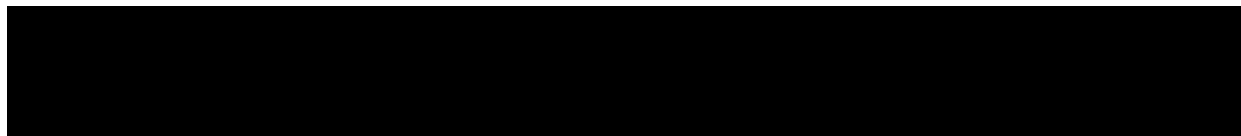
#### **6.5.5 Disposal and destruction**

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

## **7 Description of study visits**

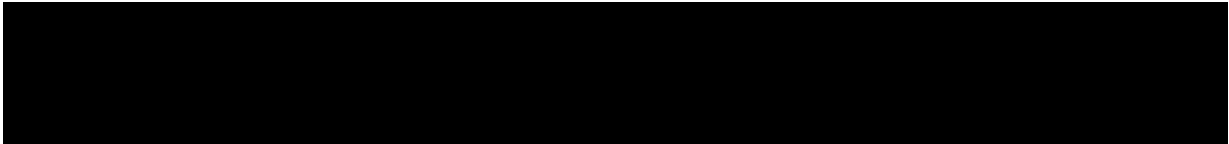
### **7.1 Schedule of observations**

[Table 7-1](#) lists all of the required assessments and indicates with an “X” the visits when they are performed. All data obtained from these assessments must be supported in the patient’s source documents. The table indicates which assessments produce data to be entered into the database (D) or remain in source documents only (S) (“Category” column).



**Table 7-1 Visit evaluation schedule**

	Category	Reference to assessment types	Screening	Baseline		Treatment Phase (± 7day Window )											
Visit Number			1	2		3	4	5	6	7	8	9	10	11	12	13	14
Day			-42 to -8	-28 to -7	-7 to -1	1*	14**	28	56	84	112	140	168	210	252	294	336
Week			-6 to -2	-4 to -2	-1	1	2	4	8	12	16	20	24	30	36	42	48
Informed Consent	S	7.1.1	X														
Inclusion/exclusion criteria	S	5.2 / 5.3	X		X												
Send a enrollment form	S				X												
Notification of the treatment start	S					X											
Demography	D	7.1.1.2	X														
Medical history / Prior medications	D	7.1.1.2	X		X												
Height	D	7.2.2.4	X														
Weight	D	7.2.2.4	X		X	X	X	X	X	X	X		X		X		X
Comprehensive physical examination	S	7.2.2.2	X										X				X
Targeted physical examination	S	7.2.2.2			X	X	X	X	X	X	X	X		X	X	X	
Measurement of spleen by palpation	D	7.2.1.2	X		X		X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	D	7.2.2.5	X		X		X	X	X	X	X		X		X		X
Vital signs	D	7.2.2.3	X		X	X	X	X	X	X	X		X		X		X
12-lead ECG	D	7.2.2.7.1	X		(X)			X		X			X				X



	Category	Reference to assessment types	Screening	Baseline		Treatment Phase (± 7day Window )											
Visit Number			1	2		3	4	5	6	7	8	9	10	11	12	13	14
Day			-42 to -8	-28 to -7	-7 to -1	1*	14**	28	56	84	112	140	168	210	252	294	336
Week			-6 to -2	-4 to -2	-1	1	2	4	8	12	16	20	24	30	36	42	48
Seven-day modified MFSAF v2.0 questionnaires	D	<a href="#">7.2.1.3</a>			X			X	X	X	X		X		X		X
EORTC QLQ-C30 questionnaires	D	<a href="#">7.2.1.3</a>			X			X		X			X				
MRI of abdomen (or CT)	D	<a href="#">7.2.1.1</a>		X						X			X		X		X
Hematology	D	<a href="#">7.2.2.6.1</a>	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry	D	<a href="#">7.2.2.6.2</a>	X		X			X	X	X	X		X		X		X
Lipid panel	D	<a href="#">7.2.2.6.5</a>			X			X		X			X				X
Coagulation	D	<a href="#">7.2.2.6.6</a>	X					X					X				X
Screening for hepatitis virus and HIV	S	<a href="#">7.2.2.6.7</a>	X														
Serum pregnancy test	D	<a href="#">7.2.2.6.4</a>	X														
Urine pregnancy test	D	<a href="#">7.2.2.6.4</a>			X			X	X	X	X	X	X	X	X	X	X
Urinalysis	D	<a href="#">7.2.2.6.3</a>			X			X					X				X

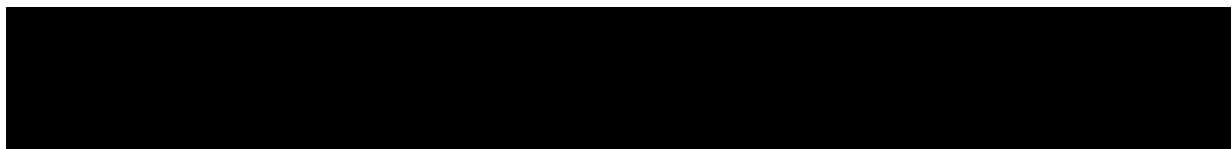
	Category	Reference to assessment types	Screening	Baseline		Treatment Phase ( $\pm$ 7day Window ) *Day1 has no time window **Only for Day14, $\pm$ 3 Day Window											
Visit Number			1	2		3	4	5	6	7	8	9	10	11	12	13	14
Day			-42 to -8	-28 to -7	-7 to -1	1*	14**	28	56	84	112	140	168	210	252	294	336
Week			-6 to -2	-4 to -2	-1	1	2	4	8	12	16	20	24	30	36	42	48
Concomitant medications	D	6.3.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Transfusion history/status	D	6.3.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	D	7.2.2.1	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense INC424	S	6.5.1				X	X	X	X	X	X	X	X	X	X	X	X
INC424 morning dose at the study site	D	7.2.3.1				X	X	X		X							
Drug accountability assessment	S	6.5.4.2					X	X	X	X	X	X	X	X	X	X	X
INC424 dosing	D	6.1				Continuous											



**Table 7-2 Visit evaluation schedule (continued)**

	Category	Reference to assessment types	INC424 dose increased or restarted (+/- 3 days)	Treatment Phase (+/- 7 days)		End of Treatment	Follow up (Study Evaluation Completion) (+10 days)
Visit Number			Extra	15, 17, 19, etc.	16, 18, 20, etc.	777	778
Day				378, 462, 546, and q12 weeks	420, 504, 588, and q12 weeks		30 days after End of Treatment
Week			2 and 4 weeks after dose increased or restarted	54, 66, 78, and q12 weeks	60, 72, 84, and q12 weeks ***only q24 weeks, e.g., 72, 96, 120 ****only q48 weeks, e.g., 96, 144, 192		
Weight	D	<a href="#">7.2.2.4</a>			X	X	X
Comprehensive physical examination	S	<a href="#">7.2.2.2</a>			X***		X
Targeted physical examination	S	<a href="#">7.2.2.2</a>	X	X	X	X	
Measurement of spleen by palpation	D	<a href="#">7.2.1.2</a>	X	X	X	X	X
ECOG performance status	D	<a href="#">7.2.2.5</a>	X		X	X	
Vital signs	D	<a href="#">7.2.2.3</a>	X		X	X	X
12-lead ECG	D	<a href="#">7.2.2.7.1</a>			X***	X	X
Seven-day modified MFSAF v2.0 questionnaires	D	<a href="#">7.2.1.3</a>			X		
MRI of abdomen (or CT)	D	<a href="#">7.2.1.1</a>			X***		

	Category	Reference to assessment types	INC424 dose increased or restarted (+/- 3 days)	Treatment Phase (+/- 7 days)		End of Treatment	Follow up (Study Evaluation Completion) (+10 days)
Visit Number			Extra	15, 17, 19, etc.	16, 18, 20, etc.	777	778
Day				378, 462, 546, and q12 weeks	420, 504, 588, and q12 weeks		30 days after End of Treatment
Week			2 and 4 weeks after dose increased or restarted	54, 66, 78, and q12 weeks	60, 72, 84, and q12 weeks ***only q24 weeks, e.g., 72, 96, 120 ****only q48 weeks, e.g., 96, 144, 192		
Hematology	D	<a href="#">7.2.2.6.1</a>	X	X	X	X	X
Serum chemistry	D	<a href="#">7.2.2.6.2</a>			X	X	X
Lipid panel	D	<a href="#">7.2.2.6.5</a>			X***		
Coagulation	D	<a href="#">7.2.2.6.6</a>			X***	X	
Serum pregnancy test	D	<a href="#">7.2.2.6.4</a>					X
Urine pregnancy test	D	<a href="#">7.2.2.6.4</a>		X	X	X	
Urinalysis	D	<a href="#">7.2.2.6.3</a>			X***	X	X



	Category	Reference to assessment types	INC424 dose increased or restarted (+/- 3 days)	Treatment Phase (+/- 7 days)		End of Treatment	Follow up (Study Evaluation Completion) (+10 days)
Visit Number			Extra	15, 17, 19, etc.	16, 18, 20, etc.	777	778
Day				378, 462, 546, and q12 weeks	420, 504, 588, and q12 weeks		30 days after End of Treatment
Week			2 and 4 weeks after dose increased or restarted	54, 66, 78, and q12 weeks	60, 72, 84, and q12 weeks ***only q24 weeks, e.g., 72, 96, 120 ****only q48 weeks, e.g., 96, 144, 192		
Concomitant medications	D	<a href="#">6.3.1</a>	X	X	X	X	X
Transfusion history/status	D	<a href="#">6.3.1</a>	X	X	X	X	X
Adverse events	D	<a href="#">7.2.2.1</a>	X	X	X	X	X
Dispense INC424	S	<a href="#">6.5.1</a>		X	X		
Drug accountability assessment	S	<a href="#">6.5.4.2</a>	X	X	X	X	
INC424 Dosing	D	<a href="#">6.1</a>	Continuous				

### **7.1.1 Screening evaluations**

Prospective participants will be scheduled for a Screening Visit by site staff. The window for this visit is Day -42 to Day -8. As noted in Inclusion criteria ([Section 5.2](#)), all drugs used to treat underlying MF must be discontinued no later than 28 days prior to the first Baseline assessment (except for the MRI scan and bone marrow examinations) for patients to enroll in the study. Site staff should inform patients to come to the study site after an overnight fast of at least 8 hours or since midnight on the day. The required Screening procedures will be scheduled to accommodate the discontinuation of prior MF medications by 28 days prior to Baseline. Informed Consent must be obtained before any study specific procedures including the discontinuation of any prior MF medications are conducted.

A patient who has a laboratory test result(s) or an ECG finding that does not satisfy the eligibility criteria may have the test(s) repeated once. These tests may be repeated as soon as the Investigator believes that the re-test result is likely to be within the acceptable range to satisfy the eligibility criteria, but should be completed within the Screening period. In this case, the patient will not be required to sign another ICF, and the original patient number assigned will be used. In the event that the laboratory test(s) cannot be performed within 5 weeks of the Screening period, or the re-test(s) do not meet the eligibility criteria or the patient's medical condition has changed significantly during the Screening period so that the eligibility criteria are no longer met, the patient is considered a Screen failure, and must be discontinued from the study. If the patient and Investigator choose to re-screen the patient, the patient must sign a new ICF, the same patient number will be assigned, and all required Screening activities must be performed when the patient is re-screened for participation in the study. An individual patient may only re-screen once for the study. Once the number of patients screened and enrolled in the study is likely to assure target enrollment, the Sponsor may, at its discretion, close the study to further screening. At this time, patients who screen fail will not be permitted to re-screen.

#### **7.1.1.1 Information to be collected on screening failures**

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

#### **7.1.1.2 Patient demographics and other characteristics**

Complete demographic information (birth date, sex, race, ethnicity, weight, and height) will be obtained at Screening along with a complete medical and medication history, and will be recorded in the appropriate eCRF.

### **7.1.2 Baseline evaluations**

The results from the Screening evaluations will be reviewed to determine if the patient continues to meet the eligibility requirements as specified in the protocol. After confirming that the patient has signed the ICF and meets all the eligibility criteria, the Investigator will

send an enrollment form to the Sponsor by fax or e-mail. The Sponsor will then notify the registration confirmation to the study site.

Procedures for the Baseline Visit may be conducted between Day -7 and Day -1 except for the MRI scan (Day -28 and Day -7) and bone marrow examinations (Day -42 and Day -1). Blood sampling for hematology (to be measured at the study site) and serum chemistry (to be measured at the central laboratory) should be performed so that the results are available before the intended Study Day 1. Patients must be reminded to arrive for the Baseline blood sample collection after an overnight fast of at least 8 hours.

The MRI scan should be conducted between Day -28 and Day -7 prior to allow ample time for the central reader to verify image quality prior to the initial administration of study drug. Image verification must be received before the patient starts study treatment. In the event that the image is determined by the central reader to have been performed incorrectly, the Baseline MRI should be rescheduled.

All evaluations should be recorded in the source documents.

### **7.1.3 On-treatment evaluations**

The Investigator or designee will notify the initiation of treatment in each patient to the Sponsor at Day 1 by fax or e-mail. On-treatment evaluations are scheduled for study visits at Day 1, and at the end of Weeks 2, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, and every 6 weeks thereafter. At the study site where hematology results are not available within the day, patients will attend the study site 1 to 3 days prior to the Visit day to provide blood samples so that the hematology results are available at the study visit. In addition, patients will visit the study site for Extra Visits to provide blood samples for hematology both 2 and 4 weeks after restarting or increasing the dose of INC424. The Extra Visit may be skipped if it takes place within 7 days of any other study visit. Blood draws for hematology at Extra Visits need not be fasted. Women of childbearing potential will be monitored regularly for pregnancy status, by urine pregnancy tests as indicated in [Table 7-1](#). If a positive urine pregnancy test occurs, a serum test should be performed to confirm the result. If local requirements mandate more frequent testing, applicable sites must adhere to these requirements even if scheduled visits are less frequent.

Between study visits, patients will self-administer INC424 twice daily as instructed, morning and evening (at approximately 12-hour intervals), in an outpatient setting. After 4 weeks of treatment (Week 4 Visit), patients may have the dose of INC424 increased because of inadequate efficacy. This efficacy assessment for dose increase at Week 4 will be based on palpable spleen length (See [Section 6.2.1.1](#)). At this visit or anytime during the study, the dose may be adjusted for safety. See [Section 6.2](#) for criteria for mandatory reduction, interruption, or discontinuation of study drug based upon results of safety monitoring. Patients should call the Investigator or designated research staff if they experience any unexpected and unfavorable signs and/or symptoms. If, at any time during the study, a patient experiences unexpected signs or symptoms, additional safety evaluations should be conducted at a regular study visit or unscheduled visit.

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 Treatment Visit, and the End of Treatment Visit procedures will be followed.

#### **7.1.4 End of treatment evaluations**

Patients who discontinue study drug should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the End of Treatment Visit ([Table 7-1](#)) will be performed. At a minimum, all patients who discontinue study treatment, including those who refuse to return for a final visit, will be contacted for safety evaluations during the 30 days following the last dose of study drug.

Patients who discontinue study treatment should be considered withdrawn from the study after the final visit assessments are performed or when it is clear that the patient will not return for these assessments.

If a study discontinuation occurs, or if the patient fails to return for visits, the Investigator must determine the primary reason for a patient's withdrawal from the study and record this information on the End of Treatment eCRF page.

##### **7.1.4.1 Criteria for end of treatment**

Patients may choose to discontinue study treatment at any time without penalty of jeopardizing their health care or loss of benefits to which the patient is otherwise entitled. Every reasonable effort should be made to determine the reason for the treatment discontinuation, which should be recorded in the eCRF.

A patient may discontinue study treatment if, in the Investigator's medical judgment, the patient is non-compliant with the study requirements.

A patient must discontinue study treatment if she becomes pregnant, or if he intends to father a child during the anticipated duration of study participation.

Patients must discontinue study treatment for one of the following reasons:

- Death
- Adverse event(s) (refer to [Section 6.2.4.2](#))
- Consent is withdrawn
- Disease progression (refer to [Section 6.2.4.1](#))
- Lost to follow-up
- Non compliance with taking study drug
- Non compliance with study procedures
- Termination of the clinical trial by the Sponsor
- New cancer therapy
- Other, i.e., if 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, further participation would be injurious to the patient's health or well being in the Investigator's medical judgment, administrative reasons

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

### **7.1.5 Follow-up evaluations**

Follow-up evaluations will be performed 30 (+10) days after the completion of the End of Treatment Visit or following the last dose of study drug. If the patient receives new cancer therapy after being withdrawn from treatment, Follow-up evaluations may be performed before 30 days following the last dose of study drug.

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, i.e., dates of telephone calls, registered letters, etc.

## **7.2 Assessment types**

### **7.2.1 Efficacy assessments**

#### **7.2.1.1 Imaging**

The primary measure of spleen size will be by MRI. MRI of the abdomen will be performed at Baseline, and at visits corresponding to Weeks 12, 24, 36, 48 and every 24 weeks thereafter for all patients on study. MRI will be performed with a body coil because the objective is to measure organ volume, not to find very small lesions. MRIs will be performed by local radiologists who will be instructed not to provide a quantitative measure of spleen volume, but may provide a qualitative assessment such as enlarged, smaller, larger, etc. However, should a quantitative result be provided to the Investigator, this will not be considered a protocol violation, and the patient will still be evaluable. The scans from an individual patient will be read by a central reader upon transfer from the site radiologist. Spleen volume will be obtained by outlining the circumference of the organ and determining the volume using the validated technique of least squares. The MRI will not determine spleen length below the costal margin, as there are no validated approaches for determining this measurement. When a post-treatment assessment indicates that a patient has experienced a  $\geq 25\%$  increase in spleen volume compared to Baseline, the Investigator will be notified from a central reader. MRI is the preferred method for obtaining spleen volume data. However, CT scans may be performed if the patient is not a candidate for MRI (because of the presence of metal clips in the body, or because of claustrophobia, for example). CT scans will be similarly processed by the same central laboratory as used for MRIs. Both for MRI and CT, procedure specific trainings for scanning and image capture will be provided by the Vendor. Generally, the same method (MRI or CT) should be used for all visits for a given patient unless a new contraindication to the use of MRI (i.e., pacemaker insertion) occurs. Please contact the Sponsor if a modality change is required.

### **7.2.1.2 Spleen length**

Spleen length will be assessed by manual palpation at the study visits indicated in [Table 7-1](#), 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 from the costal margin to the point of greatest splenic protrusion.

### **7.2.1.3 Patient reported outcomes assessment**

Patient reported outcomes regarding the impact of MF on patients will be assessed using the EORTC QLQ-C30 and Seven-day modified MFSAF questionnaires. Patients must complete the questionnaires before other clinical assessments at any given study visit.

The EORTC QLQ-C30 instructions will be provided as separate documents. The protocol assessment questionnaires should be completed in the same order and for each patient to ensure that the patient is answering these as consistently as possible.

Symptoms of MF will be assessed using Seven-day modified MFSAF v2.0. Symptoms assessed will include filling up quickly/early satiety, abdominal discomfort, abdominal pain, inactivity, night sweats, itching, and bone/muscle pain. Detailed directions for the administration of Seven-day modified MFSAF v2.0 diary will be provided in a separate document.

## **7.2.2 Safety and tolerability assessments**

Safety and tolerability assessments will consist of evaluating adverse events, laboratory parameters including hematology, chemistry and urinalysis, body weight, physical examinations, vital signs and ECG monitoring.

### **7.2.2.1 Adverse events**

Adverse events will be monitored continuously during the study. Patients will be instructed to report all adverse events during the study and patients will be assessed for the occurrence of adverse events throughout the study. All adverse events (serious and non-serious) must be recorded in the source documents and promptly entered in the eCRF regardless of the



assumption of a causal relationship with study drug. The definition, reporting, and recording requirements for adverse events are described in [Section 8.1](#).

#### **7.2.2.2 Physical examination**

A comprehensive or targeted physical examination will be performed at the study visits indicated in [Table 7-1](#). A comprehensive physical examination will include the examination of general appearance, skin, head, eyes, ears, nose, neck (including thyroid), throat, lungs, heart, abdomen (liver, spleen), back, lymph nodes, edema and extremities, vascular and neurological. In addition, the comprehensive examination will include body systems as indicated by patient symptoms, adverse events, prior physical examination, past medical history or other findings as determined by the Investigator. A targeted physical examinations will include body systems as indicated by patient symptoms, adverse events, prior physical examinations, or other findings as determined by the Investigator. The targeted examination will always include liver and spleen, and assessment of edema. Both comprehensive and targeted examinations will include a measurement of the size of spleen palpation (except Day 1). Measurement of spleen length by manual palpation will be performed as described in [Section 7.2.1.2](#).

#### **7.2.2.3 Vital signs**

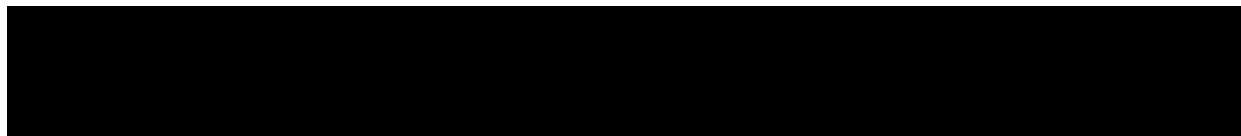
Vital signs (sitting blood pressure, sitting pulse, respiratory rate and body temperature) will be collected at the study visits indicated in [Table 7-1](#). Vital signs will be taken with the patient in the sitting position after 5 minutes of rest. Body temperature may be measured orally or via ear.

#### **7.2.2.4 Height and weight**

Height in centimeters (cm) only at Screening and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) at study visits indicated in [Table 7-1](#) will be measured.

#### **7.2.2.5 Performance status**

The performance status will be assessed according to the ECOG performance status scale ([Table 7-3](#)). For the schedule of the ECOG performance status scale assessments, see [Table 7-1](#).



**Table 7-3**      **ECOG performance status scale**

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

Source: [Oken et al. \(1982\)](#).

### 7.2.2.6 Laboratory evaluations

A central laboratory will be used for analysis of all specimens collected except for hematology, serum and urine pregnancy tests, other urine analysis and serology for hepatitis virus and HIV which will be performed locally. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to Investigators in the Laboratory Manual. For the schedule of the laboratory assessments, see [Table 7-1](#).

#### 7.2.2.6.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential including reporting of % of blasts, reticulocytes, and platelet count will be measured locally.

#### 7.2.2.6.2 Clinical chemistry

Albumin, alkaline phosphatase, ALT, amylase, AST, bilirubin (total and direct), BUN, calcium, chloride, creatinine, gamma glutamyl transferase, glucose, iron, lactate dehydrogenase, lipase, phosphorus, potassium, sodium, total protein, and uric acid will be measured. Blood samples should be collected after an overnight fast of at least 8 hours (Note: this is not required if medically contraindicated, such as certain patients with diabetes who must eat with each morning's insulin).

#### 7.2.2.6.3 Urinalysis

Urine analysis (dipstick) will be performed locally to record pH and specific gravity, bilirubin, blood, glucose, ketones, leukocytes, protein, and urobilinogen.

#### 7.2.2.6.4 Pregnancy and assessments of fertility

All women of childbearing potential will have a serum  $\beta$ -hCG test at Screening and at the last Follow-up Visit. At all other visits, the patients will have a urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study drug until serum  $\beta$ -hCG is performed and found to be negative. If positive, the patient must be discontinued from the study. All the pregnancy tests will be performed locally. Women of childbearing potential will be monitored regularly for pregnancy status, either by serum or urine pregnancy tests as described in the study schedule. If local requirements mandate more frequent testing, applicable sites must adhere to these requirements even if scheduled visits are less frequent.

#### 7.2.2.6.5 Lipid panel

Lipid panel evaluated will consist of Total cholesterol, Triglycerides, LDL, HDL, and HS-CRP will be evaluated.

#### 7.2.2.6.6 Coagulation test

Prothrombin time (PT) and partial thromboplastin time (PTT) will be measured. For PT, both time (sec) and international normalized ratio (INR) will be requested.

#### 7.2.2.6.7 Screening for hepatitis virus and HIV

IgM-HA Ab test, HBs Ag test, HBs Ab test, HBc Ab test, HCV Ab test and HIV Ab test will be evaluated at Screening. In patients who are negative for HBs Ag test but positive for either HBs Ab test or HBc Ab test, HBV-DNA test should be performed locally to check the eligibility for this study.

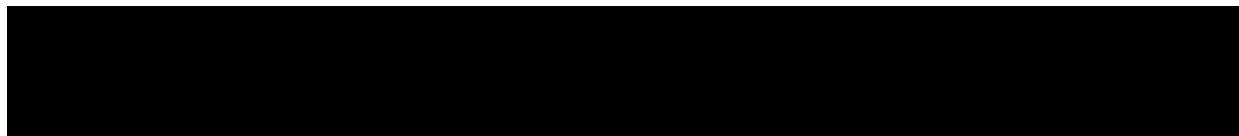
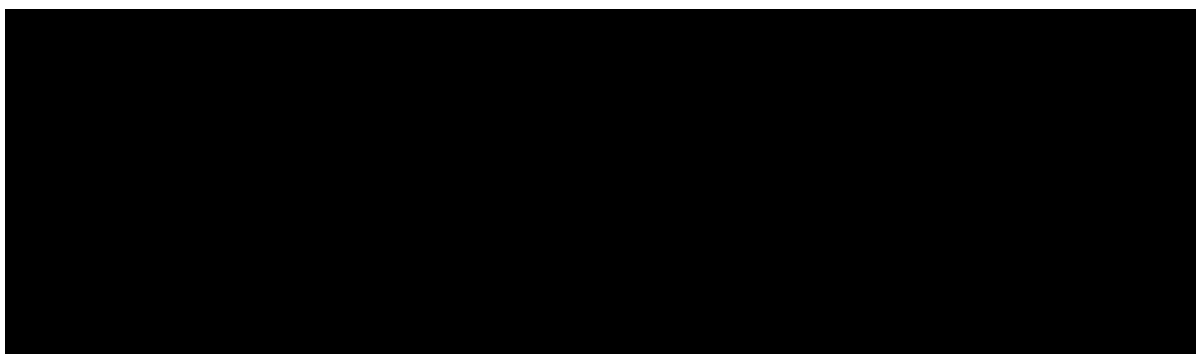
#### 7.2.2.6.8 Immunology

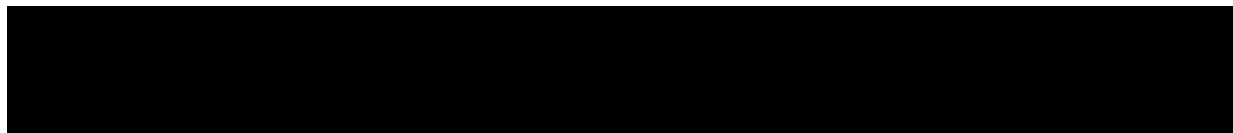
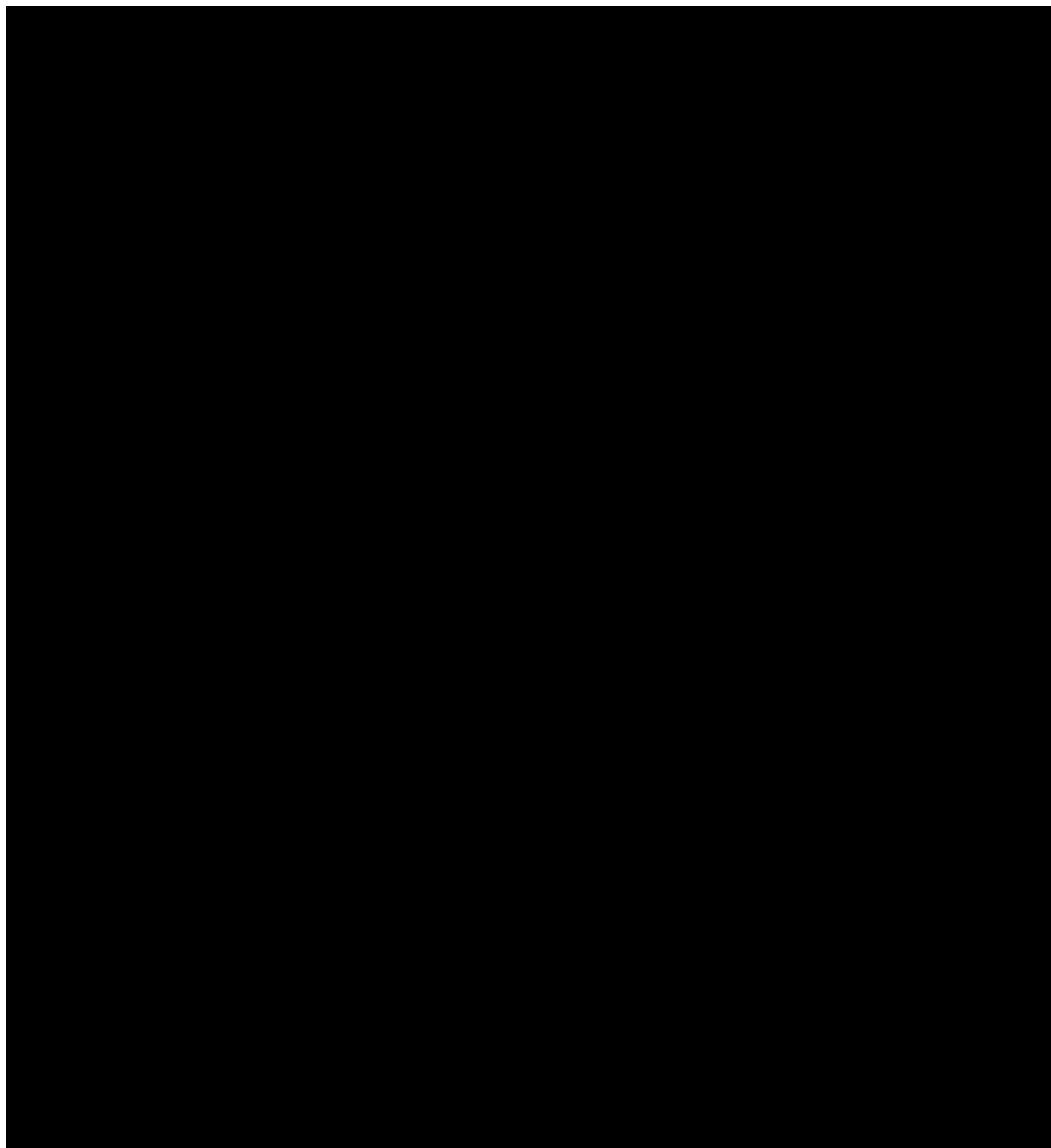
CD34+ cell count will be measured and reported as % and an absolute cell count estimated by multiplying the percentage by white blood cell count.

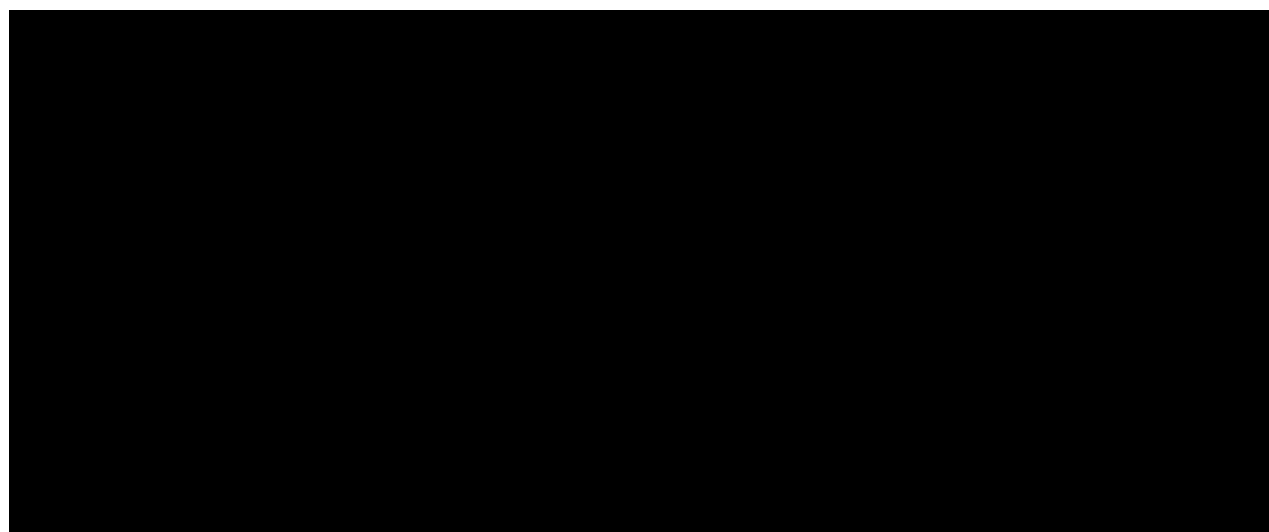
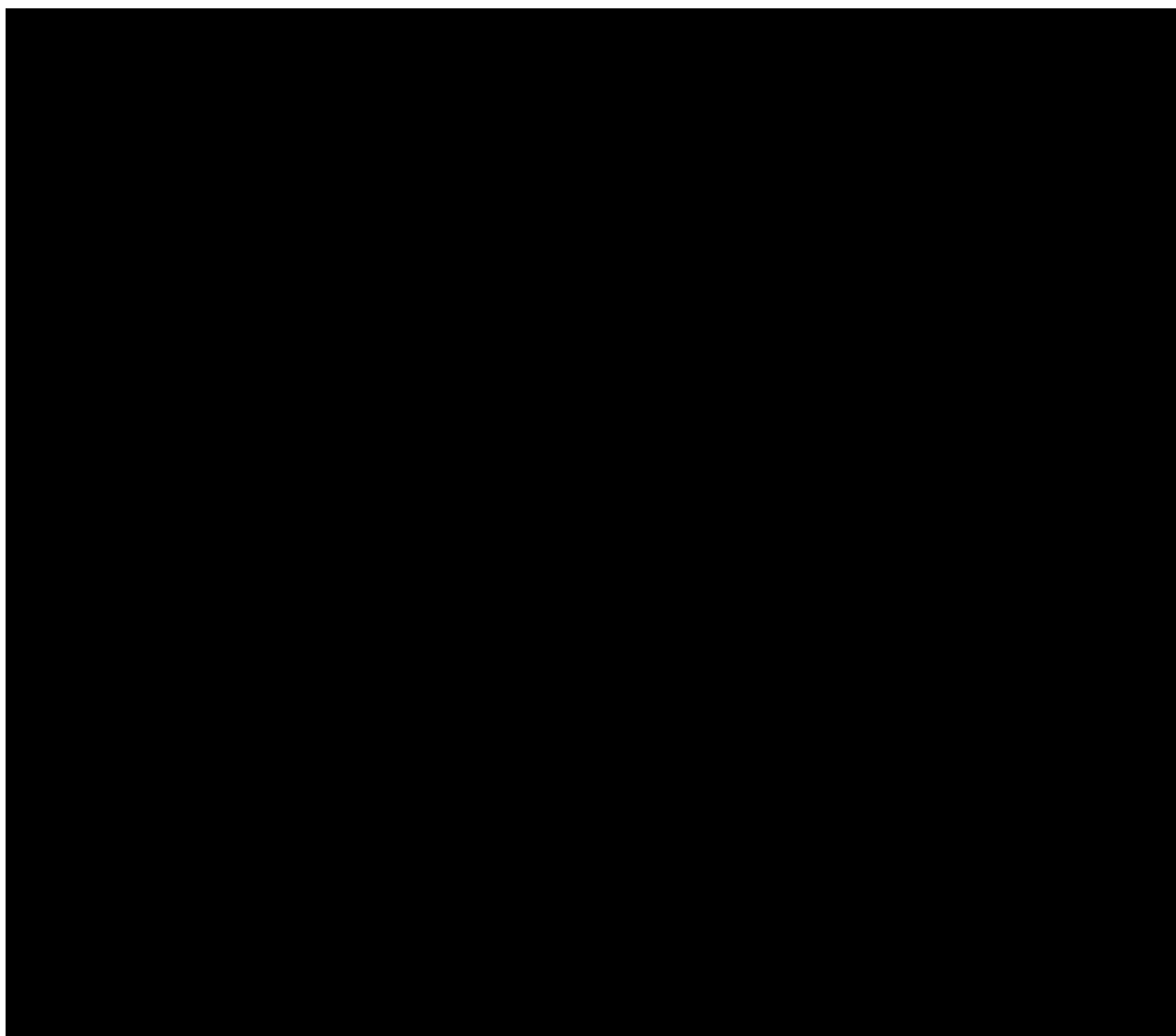
### 7.2.2.7 Cardiac assessments

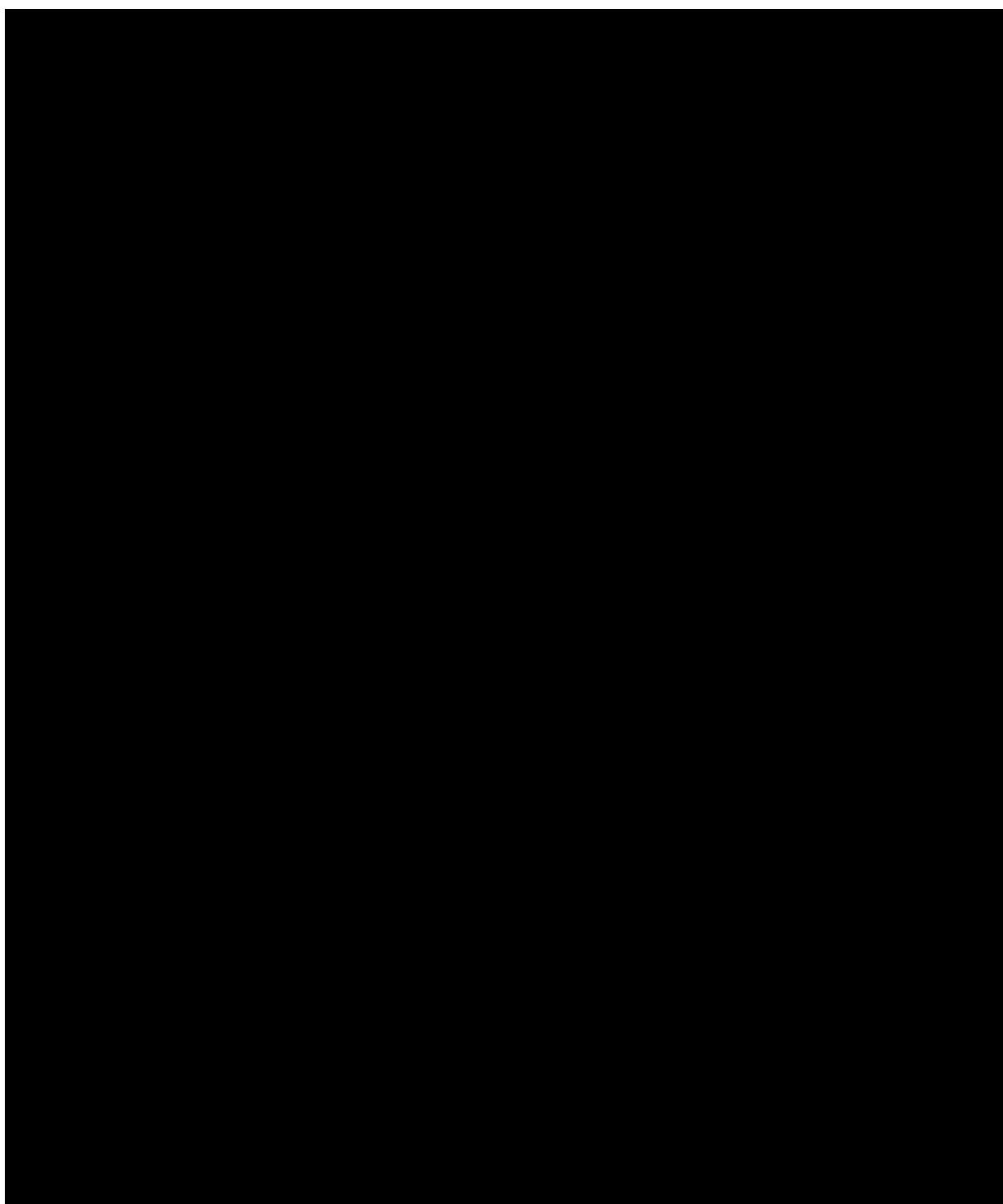
#### 7.2.2.7.1 Electrocardiogram (ECG)

Standard 12 lead ECG will be performed at study visits indicated in [Table 7-1](#). At Baseline, an ECG will be performed only if the ECG at Screening includes an abnormality deemed clinically significant. 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 after the patient signed Informed Consent except for screening failure patients should be reported on the adverse events eCRF page. Clinically significant findings must be discussed with the Sponsor 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.



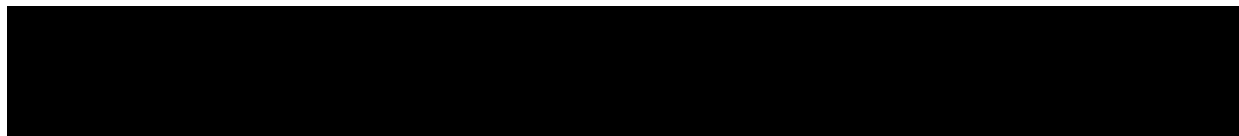






#### **7.2.5 Other assessments**

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



## **8 Safety monitoring and reporting**

### **8.1 Adverse events**

#### **8.1.1 Definitions and reporting**

An adverse event for the purposes of this protocol is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed Informed Consent has been obtained. Abnormal laboratory values or test results occurring after Informed Consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (i.e., hematologic abnormality that requires transfusion), or require changes in study drug(s).

With exception of screening failure patients, adverse events that begin or worsen after Informed Consent should be recorded in the Adverse Events eCRF. Conditions that were already present at the time of Informed Consent should be recorded in the Medical History eCRF. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute adverse events) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate adverse event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, or Grade 1-4, will be used. CTCAE Grade 5 (death) will not be used in this study; rather, information about deaths will be collected in the End of Treatment or Study Evaluation Completion eCRF page. The occurrence of adverse events should be sought by non-directive questioning of the patient during the screening process after signing Informed Consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

- The severity grade (CTCAE Grade 1-4)
- Reasonable possibility that adverse event is related to study treatment: (no, yes)
- Start and end dates, unless unresolved at final exam
- Action taken with respect to study drug (none, dose adjusted, temporarily interrupted, permanently discontinued)
- Whether it is serious, as per SAE definition provided in [Section 8.2](#).

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements, see [Section 8.2](#).

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

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

## **8.1.2 Laboratory test abnormalities**

### **8.1.2.1 Definitions and reporting**

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

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per Investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in [Section 6.2.2](#) and should not contribute to designation of a lab parameter abnormality as a SAE:

## **8.2 Serious adverse events**

### **8.2.1 Definitions**

Serious Adverse Event (SAE) is defined as one of the following:

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

### **8.2.2 Reporting**

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided Informed Consent and until at least 30 days after the patient has stopped study treatment must be reported to the Sponsor or designee within 24 hours of learning of its occurrence. Any SAEs experienced after this at least 30 day period should only be reported to the Sponsor or designee if the Investigator suspects a causal relationship to study drug. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the Investigator receiving the follow-up information. 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 drug (if there is more than one study drug), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the Sponsor.

The telephone and telefax number of the Sponsor's contact persons, specific to the site, are listed in the Investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the IB (new occurrence) and is thought to be related to the Sponsor's study drug, a Sponsor's associate may urgently require further information from the Investigator for Health Authority reporting. The Sponsor may need to issue an Investigator Notification (IN), to inform all Investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

## **8.3 Pregnancies**

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 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.

## **8.4 Warnings and precautions**

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

## **8.5 Data Monitoring Committee**

A Data Monitoring Committee (DMC) will not be established.

## **8.6 Steering Committee**

A Steering Committee (SC) will be appointed by the Sponsor. The SC will have members external to the Sponsor, Investigators participating in the trial, as well as Sponsor representatives. The SC will ensure transparent management of the study according to the protocol through the approval of modifications and recommendations as circumstances require. Together with the Sponsor representatives, the SC will also develop recommendations for publications of study results including authorship rules. Details on the SC related-procedures are summarized in the Charter.

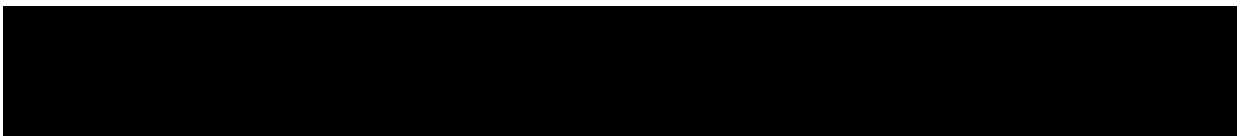
# **9 Data collection and management**

## **9.1 Data confidentiality**

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

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

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



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

## **9.2 Site monitoring**

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

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

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

## **9.3 Data collection**

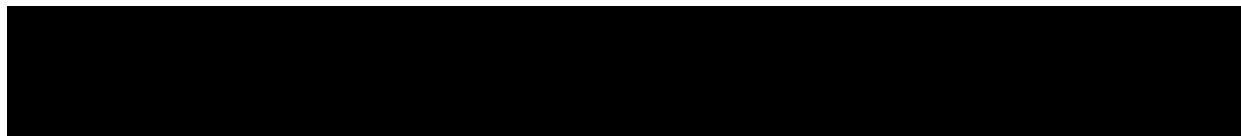
The designated Investigator staff will enter the data required by the protocol into the eCRF. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Designated Investigator site staff will not be given access to the EDC system until they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

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

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

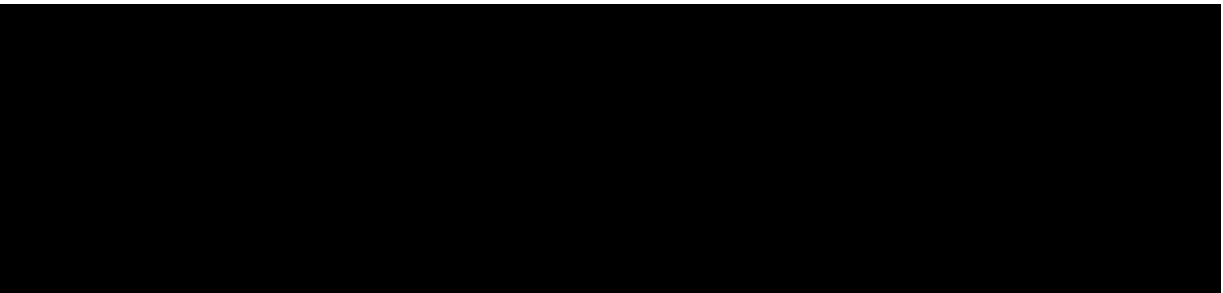
### **9.3.1 Laboratory tests**

Laboratory tests including serum chemistry, lipid panel and coagulation tests will be performed at central laboratory. The results will be transmitted electronically to a designated CRO.



### 9.3.2 Spleen imaging


The primary measure of spleen volume will be by MRI (or CT scan in applicable patients). The scans from an individual patient will be read by a central reader upon transfer from the site radiologist. MRI is the preferred method for obtaining spleen volume data. However, CT scans may be performed if the patient is not a candidate for MRI for medical contraindication. CT scans will be similarly processed by the same central laboratory as used for MRIs. Procedure specific training for scanning and image capture will be provided by the Vendor. The same method (MRI versus CT) must be used for all visits for a given patient unless a new contraindication to the use of MRI (i.e., pacemaker insertion) occurs.




### 9.4 Database management and quality control

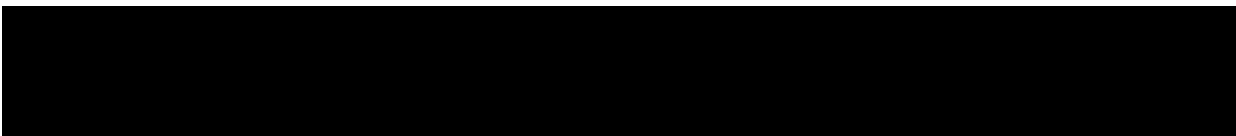
Novartis personnel or a designated CRO will review the data entered by staff at the Investigator's site for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the Investigator's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

Concomitant treatments 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.

 data of spleen imaging readings will be processed centrally and the results for patients enrolled into treatment will be sent electronically to Novartis or a designated CRO.



The occurrence of any protocol deviations will be monitored throughout the study. 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 Novartis Global Head of BDM and the Global Therapeutic Area Head.



## **10 Statistical methods and data analysis**

The cutoff date of data for the clinical study report (CSR) will be when all the patients either complete the Week 24 Visit or discontinue the study, whichever comes first. The primary analysis will be performed at that date of data cutoff. An interim analysis is planned to be performed when the first 50 patients either complete the Week 24 Visit or discontinue the study. Additionally, follow-up efficacy and safety data will also be summarized in a separate report.

### **10.1 Analysis sets**

#### **10.1.1 Full Analysis Set**

The Full Analysis Set (FAS) comprises all patients who received at least one dose of INC424.

#### **10.1.2 Safety population**

The Safety population (SAF) consists of all patients who received at least one dose of INC424 and had at least one safety evaluation post-Baseline. This analysis set will be used for all safety analyses.

#### **10.1.3 Per-Protocol Set**

The Per-Protocol Set (PPS) consists of all patients in the FAS who did not meet the criteria for major protocol deviations.

### **10.2 Patient demographics/other Baseline characteristics**

Demographic and other Baseline data (including disease characteristics) will be summarized descriptively for the FAS. Qualitative data such as sex and gender will be summarized by means of the contingency table. Quantitative data such as age and body weight will be summarized descriptively including the mean, standard deviation, median, minimum and maximum.

Medical history will be tabulated with the number and percentage of patients with medical history for each system/organ class.

All demographic and other Baseline data will also be listed.

### **10.3 Treatments (study treatment, concomitant therapies, compliance)**

The duration of exposure in days to INC424 will be defined as the time between the date of last dosing and the date of first dosing. It includes periods of temporary interruptions of INC424. The duration of exposure will be calculated for each patient, and will be summarized descriptively.

The average daily dose (mg/day) will also be calculated on a per patient basis. It is defined as the ratio of the cumulative dose to the duration of exposure. The average daily dose will be summarized descriptively.

The number and percentage of patients with dose change/dose interruption (dose change to zero mg) will be calculated by the reason for dose change.

Concomitant medications will be listed in detail and tabulated by WHO drug class.

### **10.4 Primary objective**

The primary objective is to determine the efficacy of INC424 as assessed by reduction in spleen volume.

#### **10.4.1 Variable**

The primary efficacy variable is the proportion of patients achieving  $\geq 35\%$  reduction in spleen volume from Baseline to Week 24 as measured by MRI (or CT scan).

#### **10.4.2 Statistical hypothesis, model, and method of analysis**

The primary analysis will be based on a single-sample binomial test (normal approximation) at the one-sided 2.5% significance level, analyzed in the FAS. Note that a patient with a missing spleen volume at Baseline will be excluded from the denominator in the primary efficacy analysis. A patient with a missing spleen volume at Week 24 will be considered as having not achieved the  $\geq 35\%$  reduction. Patients who drop out of the study due to any reason prior to Week 24 Visit will be considered as having not achieved the  $\geq 35\%$  reduction.

The statistical hypotheses are

$$H_0: p \leq 0.2 \text{ versus } H_1: p > 0.35,$$

where  $p$  is the proportion of patients achieving  $\geq 35\%$  reduction in spleen volume from Baseline to Week 24 as measured by MRI (or CT scan). The null hypothesis will be tested with one one-sided single-sample binomial test (normal approximation) using an overall type I error rate of 2.5%.

The study has a group sequential design and includes a single interim analysis when the first 50 patients either complete the Week 24 Visit or discontinue the study. The boundaries for the single-sample binomial test will be determined using an alpha-spending function (Lan and DeMets 1983) which approximates the boundaries of (O'Brien and Fleming 1979). For example, if exactly 50 patients are included in the interim analysis, then the p-value from the

single-sample binomial test must be  $\leq 0.001$  to be considered statistically significant. Note that the study will subsequently continue to the final analysis regardless of the statistical significance reached at the interim analysis. When 110 patients are exactly included in the final analysis, then the p-value must be  $\leq 0.024$  to be considered statistically significant. The statistical analysis will be performed using the actual numbers observed at the cut-off date for the interim and the final analyses, the corresponding boundaries will be derived from the pre-specified alpha-spending function.

#### **10.4.3 Handling of missing values/censoring/discontinuations**

Missing record for spleen volume will not be imputed.

#### **10.4.4 Supportive analyses**

An analysis on the PPS will be repeated for the primary efficacy variable.

The primary efficacy variable will be summarized within each of the following subgroups:

- Sex: male or female.
- Country: Japan, Korea, Taiwan or China.
- Baseline prognostic category: Intermediate-2 or High.
- Previous use of hydroxyurea: use or non-use.
- Starting dose: 15 mg BID or 20 mg BID.

Other subgroups may also be considered.

### **10.5 Secondary objectives**

The secondary objectives are to determine the safety of INC424 and to evaluate changes in patient reported outcomes as assessed by the EORTC QLQ-C30 score and Seven-day modified MFSAF v2.0, and to evaluate the duration of response as assessed by reduction in spleen volume.

#### **10.5.1 Change in EORTC QLQ-C30 score from Baseline to Week 24**

Data from the EORTC QLQ-C30 questionnaire will be analyzed using the standardized scores. The change from Baseline will be calculated with the data collected at the Baseline Visit as the Baseline. The 5 functional scales, 3 symptom scales, 1 global health status/QOL scales, and 6 single-item scales will be summarized with descriptive statistics by scheduled visit.

#### **10.5.2 Change in total symptom score from Baseline to Week 24 as measured by Seven-day modified MFSAF v2.0**

The change in total symptom score from Baseline will be tabulated with descriptive statistics by scheduled visit. All individual scores will also be tabulated with descriptive statistics by scheduled visit.

The percentage of patients who have  $\geq 50\%$  reduction in total symptom score at Week 24 will be estimated with 95% confidence interval.

### 10.5.3 Best response rate

The best response rate is defined as the proportion of patients achieving  $\geq 35\%$  reduction in spleen volume from Baseline at any post-baseline assessment. The best response rate will be estimated with 95% confidence interval.

### 10.5.4 Duration of maintenance of a greater or equal 35% reduction from Baseline in spleen volume

For patients who had at least one  $\geq 35\%$  reduction in spleen volume from Baseline at post-baseline, the duration of response will be calculated. The start date of the duration is defined as the first spleen volume measurement that is  $\geq 35\%$  reduction from Baseline, and the end date is defined as the earliest of the following:

- Death
- Any protocol-defined event of disease progression (see [Section 6.2.4.1](#))

Censoring date is defined as the date of the last adequate assessment of the spleen volume. Patients who had more than 1 consecutive missing spleen volume assessment will be censored at the last adequate assessment prior to the consecutive missing assessments, regardless of the occurrence of a subsequent death or any event of disease progression.

The duration of response will be evaluated using a Kaplan-Meier estimate. Note that the analysis will be performed only for patients who achieved a  $\geq 35\%$  reduction in spleen volume.

### 10.5.5 Safety

#### 10.5.5.1 Analysis set and grouping for the analyses

For all safety analyses, the SAF will be used. All listings and tables will be presented by Subject ID.

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

- Pre-treatment period: from day of patient's informed consent to the day before first dose of INC424
- On-treatment period: from day of first dose of study drug to 30 days after last dose of INC424

#### 10.5.5.2 Adverse events

Summary tables for adverse events have to include only adverse events that started or worsened during the on-treatment period, the treatment-emergent adverse events. However, all safety data (including those from the pre and post-treatment periods) will be listed and those collected during the pre-treatment are to be flagged.

The incidence of treatment-emergent adverse events (new or worsening from Baseline) will be summarized by system organ class and or preferred term, severity (based on CTCAE grades), type of adverse event, relation to study treatment. Deaths reportable as SAEs and non-fatal serious adverse events will be listed by patient and tabulated by type of adverse event.



Specific safety event categories (SEC) may be considered. Such categories consist of one or more well-defined safety events which are similar in nature and for which there is a specific clinical interest in connection with INC424. Specific SECs are to be defined by the Clinical Team with regular updates as necessary and described in the Report and Analysis plan (RAP). For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

### **10.5.5.3 Laboratory abnormalities**

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) v4.03, the study's biostatistical and reporting team will grade laboratory data accordingly. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used.

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

The following summaries will be generated separately for hematology, serum chemistry, urinary laboratory tests and coagulation:

- Frequency table for newly occurring on-treatment Grade 3 or 4
- Shift tables using CTCAE grades to compare Baseline to the worst on-treatment value
- For laboratory tests where CTCAE grades are not defined, shift tables using the low/normal/high/ (low and high) classification to compare Baseline to the worst on-treatment value.
- Listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

In addition to the above mentioned tables and listings, [REDACTED] for example figures plotting time course of raw or change in laboratory tests over time or box plots might be specified in the RAP.

### **10.5.5.4 Other safety data**

#### **12-lead ECGs**

12-lead ECGs including PR, QRS, QT, QTcF, QTcB, and RR intervals will be obtained for each patient during the study in accordance with the Schedule of Observations, and will be summarized descriptively. For the calculation of changes and percent changes in cardiac intervals, the average of intervals from the Screening and Baseline recordings will be used as the Baseline for comparison of all post-Baseline intervals.

The proportion of patients with the following outliers in QT, QTcF, or QTcB intervals will be calculated and tabulated by scheduled visit:

- A measured value of >450 ms
  - A measured value of >480 ms
  - A measured value of >500 ms
  - A change from Baseline of >30 ms
-

- A change from Baseline of >60 ms

Other ECG parameters will also be analyzed as appropriate.

### Vital signs

Vital signs including systolic blood pressure, diastolic blood pressure, respiratory rate, body temperature, and pulse will be taken in the seated position for each patient during the study.

The proportion of patients with vital signs out of the following normal ranges will be calculated:

**Table 10-1 Criteria for Clinically Notable Vital Sign Abnormalities**

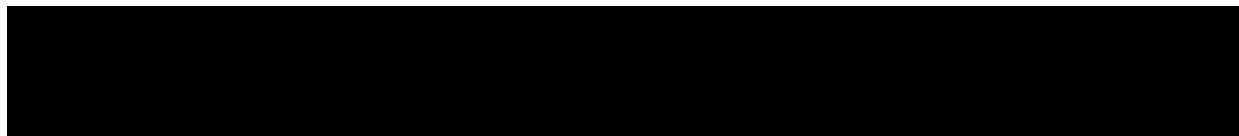
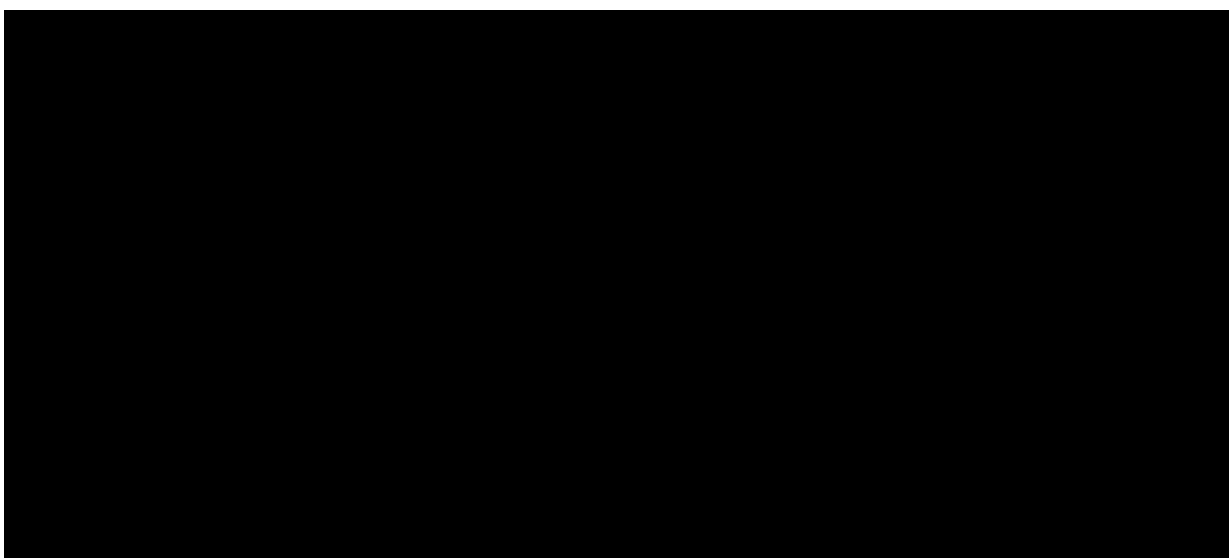
Parameter	High Threshold	Low Threshold
Systolic Blood Pressure	>160 mm Hg	<85 mm Hg
Diastolic Blood Pressure	>95 mm Hg	<50 mm Hg
Respiratory rate	> 24 per minute	< 8 per minute
Temperature	≥37.5°C	≤35.0°C
Sitting pulse	≥120 bpm	≤50 bpm

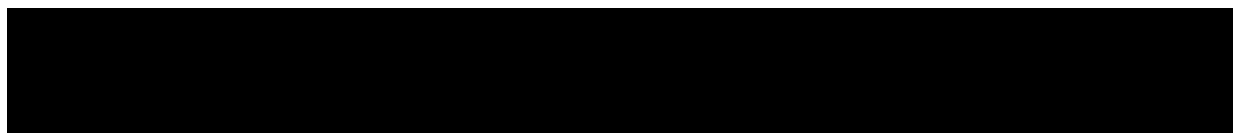
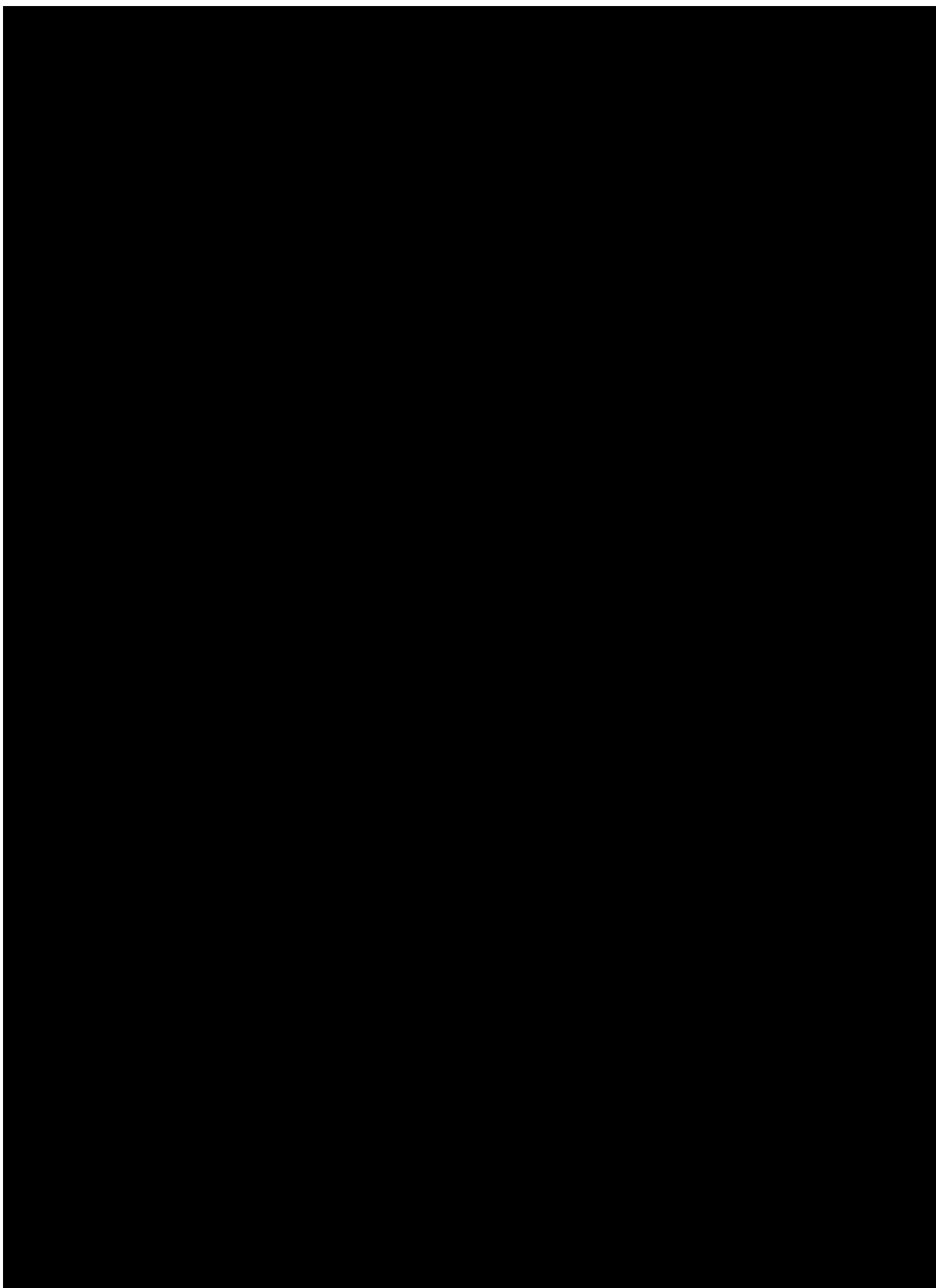
The change in weight (kg) and BMI (kg/m<sup>2</sup>) from Baseline will be summarized descriptively by scheduled visit.

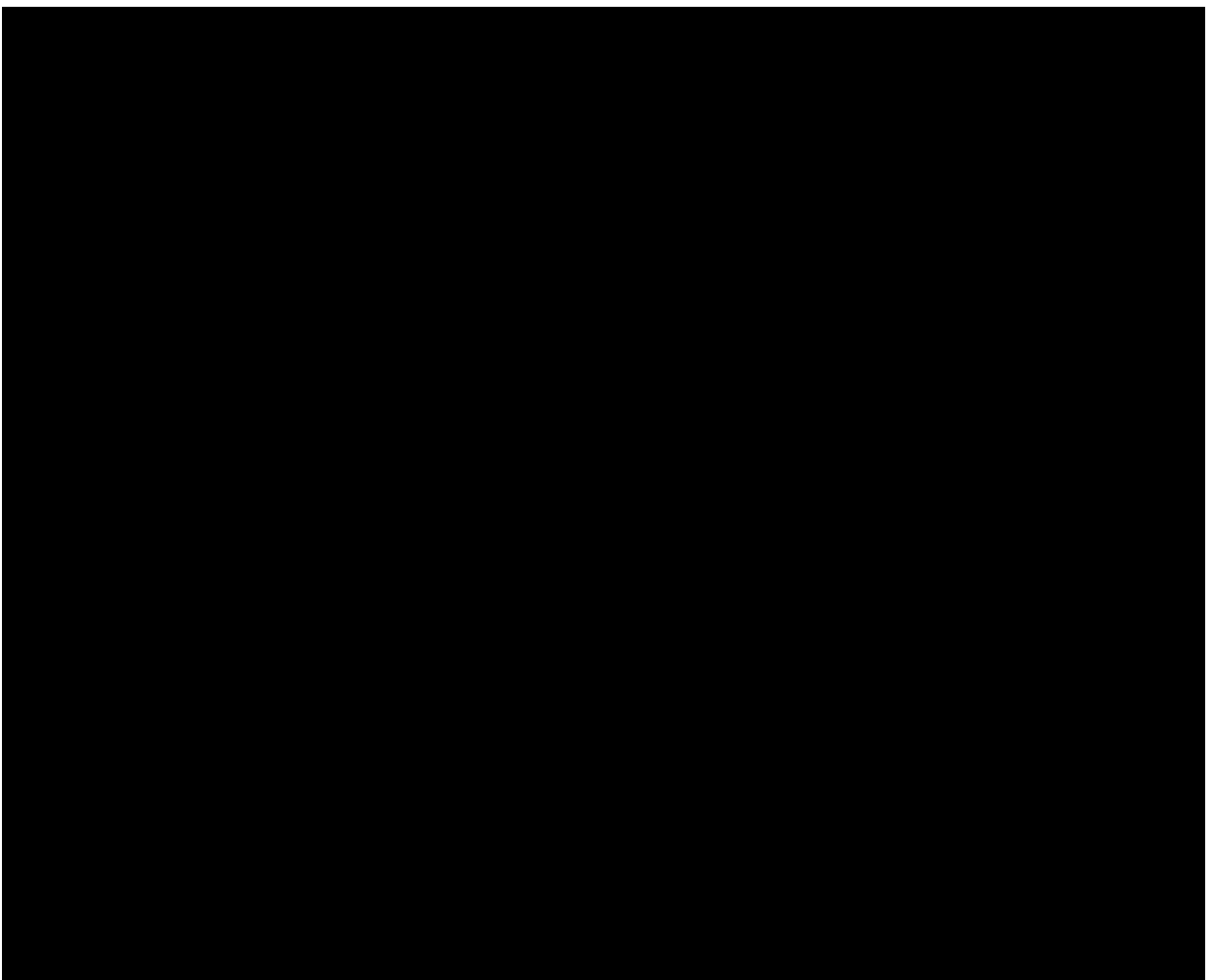
A shift table comparing Baseline with worst on-treatment result will be generated. Also, all vital signs will be listed by patient.

#### 10.5.5.5 Tolerability

The number and percentage of patients who have a dose modification due to a treatment-related adverse event will be summarized by type of dose modification (omission, dose reduction, and permanent discontinuation) and preferred term. A listing of all patients receiving INC424 who have a dosing change will include the new dose, interruption, or stopping as well as day since first dose.





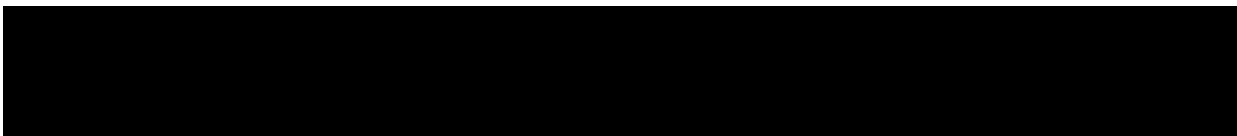


## 10.7 Interim analysis

A single interim analysis is planned to be performed when the first 50 patients either complete the Week 24 Visit or discontinue the study (information fraction is 45.5% for 110 patients, the required sample size for this study). The interim analysis will be performed to show the outstanding efficacy at the interim time-point: there is no futility look. However, note that this trial will not be stopped even if outstanding efficacy was seen at the interim time-point. The primary aim of the interim analysis is to assess the efficacy and safety of INC424 in Asian MF patients earlier and to achieve an earlier regulatory filing to health authorities with the interim efficacy and safety data. If this interim analysis shows at least the pre-specified number of responders, the Steering Committee (SC) will discuss the safety and efficacy results, and will make a final decision on the applicability of a submission.

Test boundaries will be determined using the alpha spending function described by ([Lan and DeMets 1983](#)) which approximates the boundaries of ([O'Brien and Fleming 1979](#)).

The planned study design was confirmed to fulfill the above conditions via simulations in EAST version 5.3, and the corresponding simulated probabilities and further simulation results are given in [Table 10-2](#).



**Table 10-2**      **Design properties of the proposed two stage group sequential design**

	First interim	Final analysis
Planned sample size	50	110
Information fraction (%)	45.5	100.0
Cumulative power	0.345	0.951
Stopping boundary (to reject null hypothesis)		
Z-value	3.126	1.965
Number of required responders	19	31

If the exact number of patients analyzed at the interim and final analyses deviates from 50 and 110 respectively, the actual critical boundaries will be recalculated using the alpha-spending function defined above. In particular, the critical boundary to be used at the interim analysis will be derived from the pre-specified error spending function using the actual number of patients analyzed and assuming 110 patients in the final analysis. Further, the critical value for the final analysis will be calculated using the exact number of patients analyzed at the date of data cutoff, and considering the alpha-level spent at the interim analysis, in order to achieve a cumulative type I error smaller than or equal to 2.5%.

The interim data will be analyzed by statistician in Novartis Japan BDM (Biometrics and Data Management; not independent statistician) because of open-label study and the results will be reviewed by the Steering Committee and pre-determined associates in Novartis who can have an access to the interim results. Therefore, no DMC will be established.

## 10.8 Sample size calculation

The sample size calculation was made using EAST version 5.3.

Study [INCB 18424-351] is a randomized, double-blind, placebo-controlled study comparing the efficacy and safety of INC424 to a matched placebo in patients with PMF or post-PV/ET MF. In this study, the same primary efficacy variable, i.e., proportion of patients achieving  $\geq 35\%$  reduction in spleen volume from Baseline to Week 24 as measured by MRI (or CT scan), is evaluated. The result of Study [INCB 18424-351] provided a response rate of 41.9% in INC424 group while 0.7% in placebo group.

The sample size for this study is based on the single-sample binomial test (normal approximation). Based on the results obtained in Study [INCB 18424-351], the proportion of patients on this study achieving  $\geq 35\%$  reduction in spleen volume from Baseline to Week 24 as measured by MRI (or CT scan) is expected to be 0.35. From the aspect of clinical benefit in patients with PMF or post-PV/ET MF, a threshold of 0.2 was set for null hypothesis.

An interim analysis is planned in this study. If the study had no interim analysis (1-stage approach), the required sample size of 110 provides power of 0.951 with one-sided type I error rate of 0.025 under response rate of 0.2 and 0.35 for null and alternative hypotheses. The power for the group sequential (ie, 2-stage) design accruing 110 total patients with the same final timepoint boundary ( $\geq 31/110$ ) and an interim analysis conducted after 50 patients using an O'Brien-Fleming type interim analysis boundary ( $\geq 19/50$ ) is approximately 0.95. Therefore, the effect of the interim analysis on the overall study power is negligible.

## **10.9 Power for analysis of key secondary variables**

Not applicable.

## **11 Ethical considerations and administrative procedures**

### **11.1 Regulatory and ethical compliance**

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

### **11.2 Responsibilities of the Investigator and IRB/IEC/REB**

The protocol and the proposed Informed Consent Form (ICF) 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.

### **11.3 Informed Consent procedures**

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

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

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

## **11.4 Discontinuation of the study**

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

## **11.5 Publication of study protocol and results**

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

## **11.6 Study documentation, record keeping and retention of documents**

Each participating site will maintain appropriate medical and research records for this trial, in compliance with Section 4.9 of the ICH E6 GCP, and regulatory and institutional requirements for the protection of confidentiality of patients. As part of participating in a Novartis-sponsored study, each study 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, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, and patient 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 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 eCRF 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. For electronic CRFs an audit trail will be maintained by the system. The Investigator should retain records of the changes and corrections to paper CRFs.

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

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the clinical trial unless Sponsor provides written

permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines

### **11.7 Confidentiality of study documents and patient records**

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

### **11.8 Audits and inspections**

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

### **11.9 Financial disclosures**

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

## **12 Protocol adherence**

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

### **12.1 Amendments to the protocol**

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



## 13 References (available upon request)

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## 14 Appendices

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## Appendix I - The 2008 WHO criteria for PMF, PV and ET

(Tefferi et al. 2008)

### Diagnostic criteria for PMF<sup>1</sup>

#### Major criteria

- Presence of megakaryocyte proliferation and atypia, accompanied by either reticulin or collagen fibrosis OR in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (i.e., prefibrotic cellular-phase disease)
- Not meeting WHO criteria for PV, CML, MDS or other myeloid disorders
- Demonstration of JAK2V617F or other clonal marker (i.e., MPL W515K/L) OR in the absence of the above clonal markers no evidence of secondary bone marrow fibrosis

#### Minor criteria

- Leukoerythroblastosis
- Increased serum lactate dehydrogenase level
- Anemia
- Splenomegaly

### Diagnostic criteria for PV<sup>2</sup>

#### Major criteria

- Hemoglobin >18.5 g/dL in men, >16.5 g/dL in women OR other evidence of increased red cell volume<sup>3</sup>
- Presence of JAK2V617F or other functionally similar mutation such as JAK2 exon 12 mutation

#### Minor criteria

- Bone marrow biopsy showing hypercellularity for age with trilineage myeloproliferation
- Serum erythropoietin level below the normal reference range
- Endogenous erythroid colony formation in vitro

### Diagnostic criteria for ET<sup>4</sup>

- Sustained platelet count  $\geq 450 \times 10^9/L$
- 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
- Not meeting WHO criteria for PV or PMF, BCR-ABL-positive CML, or MDS or other myeloid neoplasm
- Demonstration of JAK2V617F or other clonal marker OR in the absence of JAK2V617F, no evidence of reactive thrombocytosis

WHO = World Health Organization, PMF = primary myelofibrosis, PV= polycythemia vera, CML = chronic myeloid leukemia, ET = essential thrombocythemia, MDS = myelodysplastic syndrome

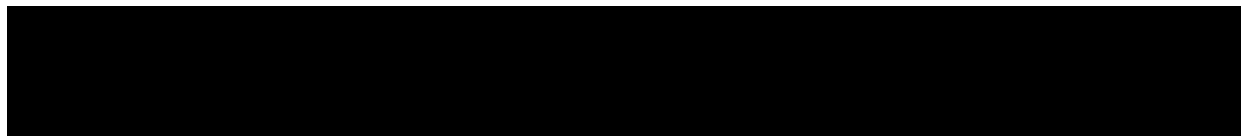
<sup>1</sup>Diagnosis of PMF requires all three major criteria and two minor criteria.

<sup>2</sup>Diagnosis of PV requires meeting either both major criteria and one minor criterion OR the first major criterion and two minor criteria.

<sup>3</sup>Hemoglobin or hematocrit >99th percentile of reference range for age, sex or altitude of residence OR red cell mass >25% above mean normal predicted or hemoglobin >17 g/dL (men) or >15 g/dL

(women) if associated with a sustained increase of  $>2$  g/dL from Baseline that cannot be attributed to correction of iron deficiency.

<sup>4</sup>Diagnosis of ET requires all four criteria.



## Appendix II- IWG-MRT recommended criteria for post-PV/ET MF

(Barosi et al. 2008)

### Diagnostic criteria for post-PV MF<sup>1</sup>

#### Required criteria

- Documentation of a previous diagnosis of PV as defined by the WHO criteria
- Bone marrow fibrosis Grade 2-3 (on 0-3 scale)<sup>2</sup> or Grade 3-4 (on 0-4 scale)<sup>3</sup>

#### Additional criteria

- Anemia<sup>4</sup> or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
- A leukoerythroblastic peripheral blood picture
- Increasing splenomegaly defined as either an increase in palpable splenomegaly of  $\geq 5$  cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
- Development of  $\geq 1$  of three constitutional symptoms:  $>10\%$  weight loss in 6 months, night sweats, unexplained fever ( $>37.5$  °C)

### Diagnostic criteria for post-ET MF<sup>5</sup>

#### Required criteria

- Documentation of a previous diagnosis of ET as defined by the WHO criteria
- Bone marrow fibrosis Grade 2-3 (on 0-3 scale)<sup>2</sup> or Grade 3-4 (on 0-4 scale)<sup>3</sup>

#### Additional criteria

- Anemia<sup>4</sup> and a  $\geq 2$  g/dL decrease from Baseline hemoglobin level
- A leukoerythroblastic peripheral blood picture
- Increasing splenomegaly defined as either an increase in palpable splenomegaly of  $\geq 5$  cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly
- Increased LDH (above reference level)
- Development of  $\geq 1$  of three constitutional symptoms:  $>10\%$  weight loss in 6 months, night sweats, unexplained fever ( $>37.5$  °C)

IWG-MRT = International Working Group for Myelofibrosis Research and Treatment, PV= polycythemia vera, ET = essential thrombocythemia, MF = myelofibrosis, WHO = World Health Organization, LDH = lactate dehydrogenase

<sup>1</sup>Diagnosis of post-PV MF requires all required criteria and two additional criteria.

<sup>2</sup>Grade 2-3 according to the European classification (Thiele et al. 2005): 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).

<sup>3</sup>Grade 3-4 according to the standard classification (Manoharan et al. 1979): 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.

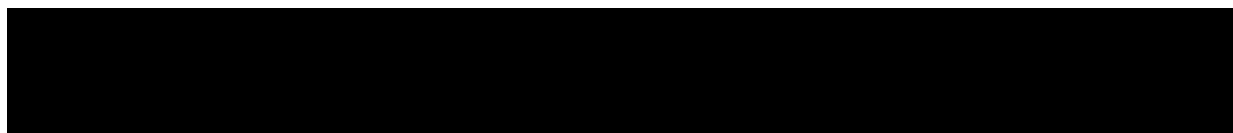
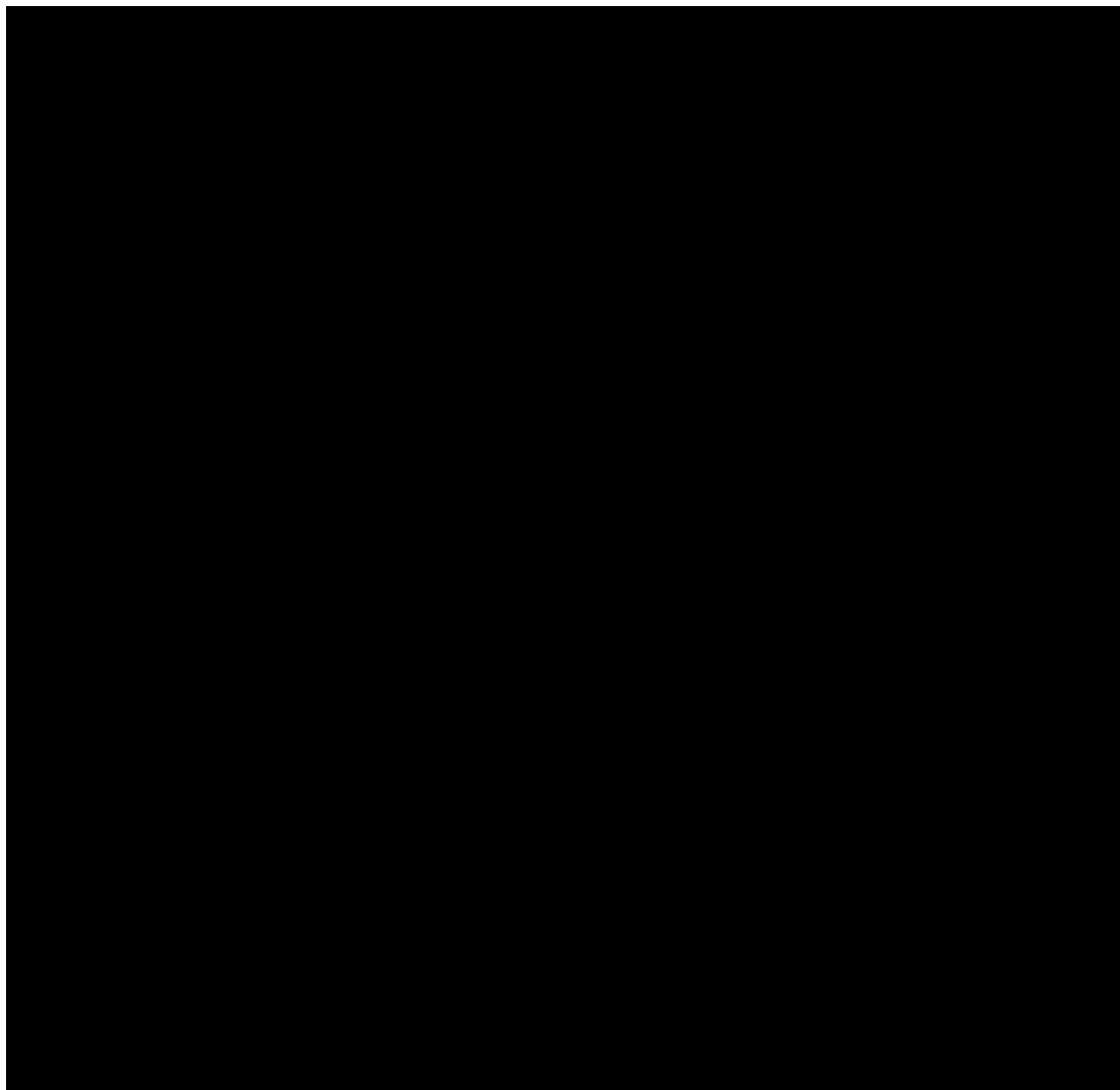
<sup>4</sup>Below the reference range for appropriate age, sex, gender and altitude considerations.

<sup>5</sup>Diagnosis of post-ET MF requires meeting all required criteria and two additional criteria.

### **Appendix III - Information regarding effectiveness of contraceptive methods**

For patients participating in the study, female patients will be required to use highly effective contraception as described below. The duration of contraception in case highly effective contraception is required is during dosing and for 5 times the terminal  $t_{1/2}$  (about 15 hours).

- Total abstinence
- Sterilization
- Combination of any two of the following (a+b OR a+c OR b+c):
  - a. Use of oral, injected or implanted hormonal methods of contraception
  - b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  - c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository





## Appendix V - Restricted/prohibited medications

These medications are restricted or prohibited in combination with INC424:

### Restricted medications

Use of all CYP3A4 inhibitors or inducers is discouraged as they may have effects on plasma levels of INC424. Alternative therapies should be considered, if available.

CYP3A4 inhibitors	CYP3A4 inducers	Other restricted therapies
<p>Strong<sup>1</sup></p> <ul style="list-style-type: none"> <li>clarithromycin</li> <li>itraconazole</li> <li>ketoconazole</li> <li>nefazodone</li> <li>telithromycin</li> </ul> <p>Moderate</p> <ul style="list-style-type: none"> <li>aprepitant</li> <li>erythromycin</li> <li>fluconazole</li> <li>grapefruit juice</li> <li>verapamil</li> </ul> <p>Weak to Moderate</p> <ul style="list-style-type: none"> <li>diltiazem</li> </ul> <p>Weak</p> <ul style="list-style-type: none"> <li>cimetidine</li> </ul> <p>All other inhibitors;</p> <ul style="list-style-type: none"> <li>amiodarone</li> <li>chloramphenicol</li> <li>delaviridine</li> <li>diethyl-dithiocarbamate</li> <li>fluvoxamine</li> <li>gestodene</li> <li>imatinib</li> <li>mibefradil</li> <li>mifepristone</li> <li>norfloxacin</li> <li>norfluoxetine</li> <li>starfruit</li> <li>voriconazole</li> </ul>	<p>Weak to moderate</p> <ul style="list-style-type: none"> <li>barbiturates</li> <li>carbamazepine</li> <li>glucocorticoids</li> <li>modafinil</li> <li>nevirapine</li> <li>oxcarbazepine</li> <li>phenobarbital</li> <li>phenytoin</li> <li>pioglitazone</li> <li>rifabutin</li> </ul>	<ul style="list-style-type: none"> <li>Aspirin is permitted only below 150mg/day; acetaminophen or ibuprofen may be used</li> <li>Hematopoietic growth factor receptor agonists (i.e., erythropoietin) or granulocyte colony stimulating factor (romiplostim, eltrombopag) are not recommended; they may result in an increase in spleen size, and study drug efficacy may be compromised</li> <li>Anti-coagulant/anti-platelet medications should be administered with careful consideration of any thrombocytopenia</li> </ul>
<p><sup>1</sup>Dose modification of INC424 is required if any of these medications are used concomitantly with INC424 (see <a href="#">Section 6.2.3</a>).</p>		

### **Prohibited medications**

Systemic steroids (i.e. prednisone >10 mg)

Aspirin >150 mg/day

Any other investigational medication

Any other medication for myelofibrosis: hydroxyurea, busulfan, interferon, lenalidomide, thalidomide, anagrelide

Potent CYP3A4 Inducers: rifampin St. John's Wort