NOVARTIS

Clinical Development

INC424/ruxolitinib/Jakavi®/

CINC424A2202 / NCT01392443

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

Statistical Analysis Plan (SAP) for final CSR

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List of abbreviations

AE	Adverse Event
bpm	Beats per minute
AESI	Adverse Events of special interest
CRS	Compound Case Retrieval Strategy' Sheet
CSR	Clinical Study Report
CT	Computer Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DI	Dose Intensity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EORTC	European Organization for Research and Treatment of Cancer
FAS	Full Analysis Set
IWG-MRT	International Working Group for Myelofibrosis Research and Treatment
MedDRA	Medical Dictionary for Regulatory Affairs
MF	Myelofibrosis
MFSAF	Myelofibrosis Symptom Assessment Form
MRI	Magnetic Resonance Imaging
ms	Millisecond
[redacted]	[redacted]
PD	Protocol Deviation
PD	Pharmacodynamics
PET-MF	Post Essential Thrombocytemia-Myelofibrosis
PK	Pharmacokinetic
PMF	Primary Myelofibrosis
PPS	Per-Protocol Set
PPV-MF	Post Polycythemia Vera-Myelofibrosis
PT	Preferred Term
QoL	Quality of Life
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SI	Standard International
SMQ	Standard MedDRA Query
SOC	System Organ Class
WBC	White Blood Cell

1 Introduction

This statistical analysis plan (SAP) describes all planned analyses for the final Clinical Study Report (CSR) of study CINC424A2202, a phase II, open-label, multi-center study of the JAK inhibitor INC424.

A single interim analysis was conducted when the first 50 patients had completed the Week 24 visit or discontinued from the study prior to the Week 24 visit. The aim of the interim analysis was 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. The efficacy, safety [redacted] analyses have been performed for 120 patients since the interim analysis showed the positive result. The analysis plan of CSR for Week 24 was documented in "CINC424A2202 RAP Module 3 Detailed statistical methodology Amendment 2" and the results were presented in "the Week 24 CSR" released on Sep 4 2013.

1.1 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 is conducted in four Asian countries, i.e., China, Japan, Korea and Taiwan.

1.2 Study objectives and endpoints

Table 1-1 shows objectives and endpoints for this study.

Table 1-1 Objectives and endpoints

	Objective	Endpoint
Primary	To determine the efficacy of INC424 as assessed by reduction in spleen volume	Proportion of patients achieving ≥35% reduction in spleen volume from Baseline to Week 24 as measured by MRI (or CT scan in applicable patients)
Secondary	To determine the safety and tolerability of INC424	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.
Secondary	To evaluate the effects of INC424 on patient reported outcomes	Change in EORTC QLQ-C30 score from Baseline to Week 24.
		Change in total symptom score from Baseline to Week 24, as assessed by

	Objective	Endpoint
		Seven-day modified MFSAF v2.0
Secondary	To evaluate the duration of response as assessed by reduction in spleen volume	Best response rate
		Duration of maintenance of a ≥35% reduction from Baseline in spleen volume

2 Statistical methods

2.1 Data analysis general information

The final CSR analysis will be performed by Novartis. SAS® version 9.4 (or later version if available at time of database lock) will be used to perform all data analyses and to generate tables, figures and listings.

Unless otherwise specified, categorical data will be summarized by frequency count and percentages. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.

The final analysis will be performed after final Data Base Lock (DBL).

2.1.1 General definitions

Study drug and study treatment

Both study drug and study treatment refer to INC424.

Date of first administration of study drug

The date of first administration of study drug is defined as the first date when a nonzero dose of study drug is administered and recorded on the dose administration record (DAR) page of the electronic case report form (eCRF).

Date of last administration of study drug

The date of last administration of study drug is defined as the last date when a nonzero dose of study drug is administered and recorded on DAR page of the eCRF.

Study day

Study day 1 is the date of first administration of study drug.

The study day for all assessments will be calculated as follows:

1. If date of assessment occurred on or after the start of study treatment, then

   Study day = Date of assessment - Start date of study treatment + 1.

2. If date of assessment occurred before the start of study treatment, then

   Study day = Date of assessment - Start date of study treatment.

The study day will be displayed in the data listings.

Baseline

Unless otherwise specified, the baseline measurement for any parameter is defined as the last non-missing pre-dose value (scheduled or unscheduled) before the first administration of study drug.

On-treatment assessment/event

On-treatment period is from day of first dose of study drug to 30 days after last dose of INC424.

2.2 Analysis sets

Full Analysis Set (FAS)

FAS comprises all patients who received at least one dose of INC424.

Safety set (SAF)

Safety set 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.

Per-Protocol Set (PPS)

PPS consists of all patients in the FAS who are considered to be sufficiently compliant with the protocol.

2.2.1 Subgroup of interest

All results by subgroups were reported in “the Week 24 CSR” and not applicable in this document.

2.3 Patient disposition, demographics and other baseline characteristics

2.3.1 Patient disposition

Patient disposition will be summarized using FAS.

2.3.2 Demographics and baseline data

Summary of all baseline and demographics were reported in "the Week 24 CSR" and not applicable in this document.

2.3.3 Medical history and current medical conditions

Summary of relevant medical history and current medical conditions were reported in "the Week 24 CSR" and not applicable in this document.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure/follow-up and dose intensity (DI)

The duration of exposure is defined as the time from first (non-zero) dose to the last date patient was known to have been taking study drug (i.e., last known treatment date).

That is, the following algorithm will be used to calculate the duration of exposure for patients who took at least one dose of the study drug:

- Duration of exposure (days) = [(date of last administration of study drug) – (date of first administration of study drug) + 1]

The duration includes the periods of temporary interruption.

The duration of exposure will also be summarized using week/month as time unit. They will be calculated as [Duration of exposure in days] divided by 7/30.4375.

Cumulative dose is defined as the total dose given during the study treatment exposure. Dose intensity (DI) is defined as:

DI (mg/day) = Cumulative dose given (mg) / Duration of exposure (days).

Cumulative dose and dose intensity will be calculated using descriptive statistics.

Dose intensity will be plotted by week.

Relative dose intensity will be defined as follows:

Relative dose intensity (%) = DI*100/Assigned total daily dose (i.e. starting dose)

A plot of mean daily total dose over time by starting dose will be generated for the overall population.

Relative dose intensity and dose intensity will be summarized using descriptive statistics by time-interval and starting dose(15 mg BID or 20 mg BID).

A line graph of mean daily total dose over time by starting dose will be generated for the overall population.

Dose reduction/interruption

The number and percentage of patients with at least one dose reduction and dose interruption (dose change to zero dose for limited duration) will be calculated, respectively. The associated reasons for dose reduction and dose interruption will be summarized separately.

2.4.2 Prior, concomitant and post therapies

Concomitant medication and significant non-drug therapies before/after the start of study drug were reported in "the Week 24 CSR" and not applicable in this document.

2.5 Analysis of the primary objective

Primary analysis was conducted and the result was reported in "the Week 24 CSR" and not applicable in this document.

2.6 Analysis of the key secondary objective

Not Applicable.

2.7 Analysis of secondary efficacy objective(s)

Most secondary analyses were reported in "the Week 24 CSR" and not applicable in this document. The below analyses which were previously performed will be repeated with updated data for the final analysis.

Best response rate

The best response rate is defined as the proportion of patients achieving ≥ 35% reduction in spleen volume from Baseline at any post-baseline assessment. The best response rate will be estimated with an associated 95% confidence interval based on the normal approximation.

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

For patients who had at least one ≥ 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 ≥ 35% reduction from Baseline, and the end date of the response duration is defined as the earliest of the following:

- Death.
- A ≥ 25% increase in spleen volume by MRI compared to Baseline.
- Splenic irradiation.

- Leukemic transformation as defined by a bone marrow or a peripheral blood blast count of ≥ 20%.
- Splenectomy.

In the event that a patient experiences leukemic transformation, requires therapy with splenic irradiation, or experiences a ≥ 25% increase in spleen volume by MRI compared to Baseline, the study drug must be permanently discontinued. Therefore, the end date of the duration will be defined as the earliest date for one of the following for patient with any event of disease progression:

- Date of death.
- Assessment date of spleen volume with a ≥ 25% increase compared to Baseline measured by MRI.
- Date of leukemic transformation captured on the e-CRF page "Leukemic transformation".
- Date of Splenic irradiation/Splenectomy captured on either the "Concomitant medications/Significant non-drug therapies" or "Antineoplastic therapies since discontinuation of study drug" e-CRF pages.

If a patient undergoes splenectomy, and the investigator believes that it is in the patient's best interest to continue treatment with INC424 due to symptomatic improvement, the patient may continue treatment assuming she/he has fully recovered from the splenectomy procedure within 12 weeks. Even if she/he continues therapy with INC424, the event will be assumed to have occurred for that patient. Note that the date of splenectomy will be recorded on the e-CRF page "Concomitant medications/Significant non-drug therapies" if that patient continues treatment with INC424.

The censoring date is defined as the date of the last adequate assessment of spleen volume for patients with no event of disease progression. 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 least one ≥ 35% reduction in spleen volume at any time on study.

2.8 Safety analyses

For all safety analyses, the safety set will be used.

2.8.1 Adverse events (AEs)

In this study, an adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after a patient's signed Informed Consent has been obtained. With exception of screening failure patients, adverse events that begin or worsen after Informed Consent will be recorded in the Adverse Events eCRF.

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. Listings will include all reported AEs in the database (except AEs that started after the study completion date) and such AEs that have an onset prior to Study Day 1 are to be flagged in the listing.

Both system organ class (SOC) and preferred term (PT) as listed by the Medical Dictionary for Regulatory Activities (MedDRA, the latest version) will be used for all AE summaries. The following summaries will be produced:

- Overall summary of adverse events
- Adverse events, regardless of study drug relationship, by primary system organ class
- Adverse events, regardless of study drug relationship, by preferred term
- Adverse events, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events, regardless of study drug relationship, by study period, primary system organ class and preferred term
- Adverse events suspected to be related to study drug, by preferred term
- Adverse events suspected to be related to study drug, by primary system organ class and preferred term
- Serious adverse events, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events leading to discontinuation, regardless of study drug relationship, by preferred term
- Adverse events leading to discontinuation, regardless of study drug relationship, by primary system organ class and preferred term
- Adverse events leading to dose adjustment or study drug interruption, regardless of study drug relationship, by preferred term
- Adverse events leading to dose adjustment or study drug interruption, regardless of study drug relationship, by primary system organ class and preferred term

Clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov, the following summaries will be produced:

- On-treatment AEs (i.e., treatment-emergent AEs) which are not serious AEs with an incidence greater than 5% and on on-treatment serious AEs by primary system organ class and preferred term
- Serious AEs suspected to be related to study treatment by primary system organ class and preferred term

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same system organ class and preferred term:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one serious AE / serious AE suspected to be related to study treatment / non-serious AE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one serious AE is occurring, then one occurrence is calculated for that serious AE.

The number of deaths resulting from serious AEs suspected to be related to study treatment and serious AEs irrespective of study treatment relationship will be provided by primary system organ class and preferred term.

2.8.1.1 Adverse events of special interest / grouping of AEs

The following Adverse Events of special interest (AESIs) will be defined:

- Thrombocytopenia
- Erythropenia (Anemia)
- Leukopenia
- Hemorrhage (all AEs)
- Hemorrhage (Bruising)
- Hemorrhage (GI bleeding)
- Hemorrhage (Intracranial haemorrhage)
- Hemorrhage (Other hemorrhage events)
- Herpes zoster
- Urinary tract infections
- Tuberculosis
- Opportunistic infections
- Pneumonia
- Sepsis and septic shock
- Other infections
- Infections and infestations (SOC)
- Infections and infestations (SOC) without tuberculosis
- Elevated transaminases
- Malignancies
- Progressive multifocal leukoencephalopathy (PML)
- Dizziness
- Weight gain
- Non-melanoma skin cancer (NMSC)
- Hepatitis B reactivation (possible)
- Lipid abnormalites
- Ischemic events
- Hypertension (SMQ)

Selection rules are documented in the ‘Compound Case Retrieval Strategy’ Sheet (CRS) MedDRA 20.0 version 1.0 (or later version if available at the time point of output generation).

The following summary will be done for each AESI group:

- Overall summary of adverse events of special interest

The following summaries also will be done for each SMQ: Erythropenia, Thrombocytopenia and Leukopenia:

- Time to first newly reported grade 3 or 4
- Duration of newly reported grade 3 or 4

2.8.2 Deaths

On-treatment deaths will be displayed and all deaths will be listed.

2.8.3 Laboratory data

Clinical laboratory tests including hematology, clinical chemistry, urinalysis, lipid panel, coagulation test, and immunology will be done for each patient during the study in accordance with the 'Visit Evaluation Schedule' described in the protocol. If specific safety issue arise, additional, unscheduled laboratory tests/analyses may be done at the discretion of the investigators. A central laboratory will be used for analysis of all specimens collected except for hematology, pregnancy tests, other urine analysis and serology for hepatitis virus and HIV which will be performed locally.

Laboratory data reported will be graded by programming based on the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.3, where applicable. A severity grade of 0 will be assigned when the value is within normal limits. (In the case when a laboratory normal range overlaps into the higher (i.e., non-zero) CTC grade, the laboratory value will still be taken as within normal limits and assigned a CTC grade of zero.) Some parameters may be converted in Standard International (SI) units if laboratory measurement with any other unit was reported. For the summarization of laboratory measurements and listing of laboratory measurements, SI unit will be used as default with original or converted measurements. 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 summary will be produced for laboratory parameters in hematology:

- Shift tables using CTC grades to compare baseline to the worst on-treatment value

All laboratory data will be listed with updated data for the final analysis. Patient with abnormal hematology values will be also listed.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

12-lead ECGs including QTcF, QTcB, QT, HR, PR, QRS and RR will be measured for each patient during the study in accordance with the Visit Evaluation Schedule, and will be summarized descriptively. For the calculation of absolute change 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 overall interpretation of abnormality (Table 2-1) will be presented.

Table 2-1 Notable electrocardiogram values

Parameters	Type of abnormality	Criterion
QT, QTcF and QTcB	Change from Baseline New absolute value	Increase > 30 ms to ≤ 60 ms Increase > 60 ms > 450 ms to ≤ 480 ms > 480 ms to ≤ 500 ms > 500 ms
HR	Change from Baseline	Decrease > 25% and resultant HR < 50 bpm Increase > 25% and resultant HR > 100 bpm
PR	Change from Baseline	Increase > 25% and resultant PR > 200 ms Decrease >25% and resultant PR <75 ms
QRS	Change from Baseline	Increase > 25% and resultant QRS > 110 ms Decrease >25 % and resultant QRS < 50 ms

All abnormalities recorded on the e-CRF will be listed by patient. Also, all ECGs will be listed with updated data for the final analysis.

2.8.4.2 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.

Criteria for abnormal vital signs is given in Table 2-2.

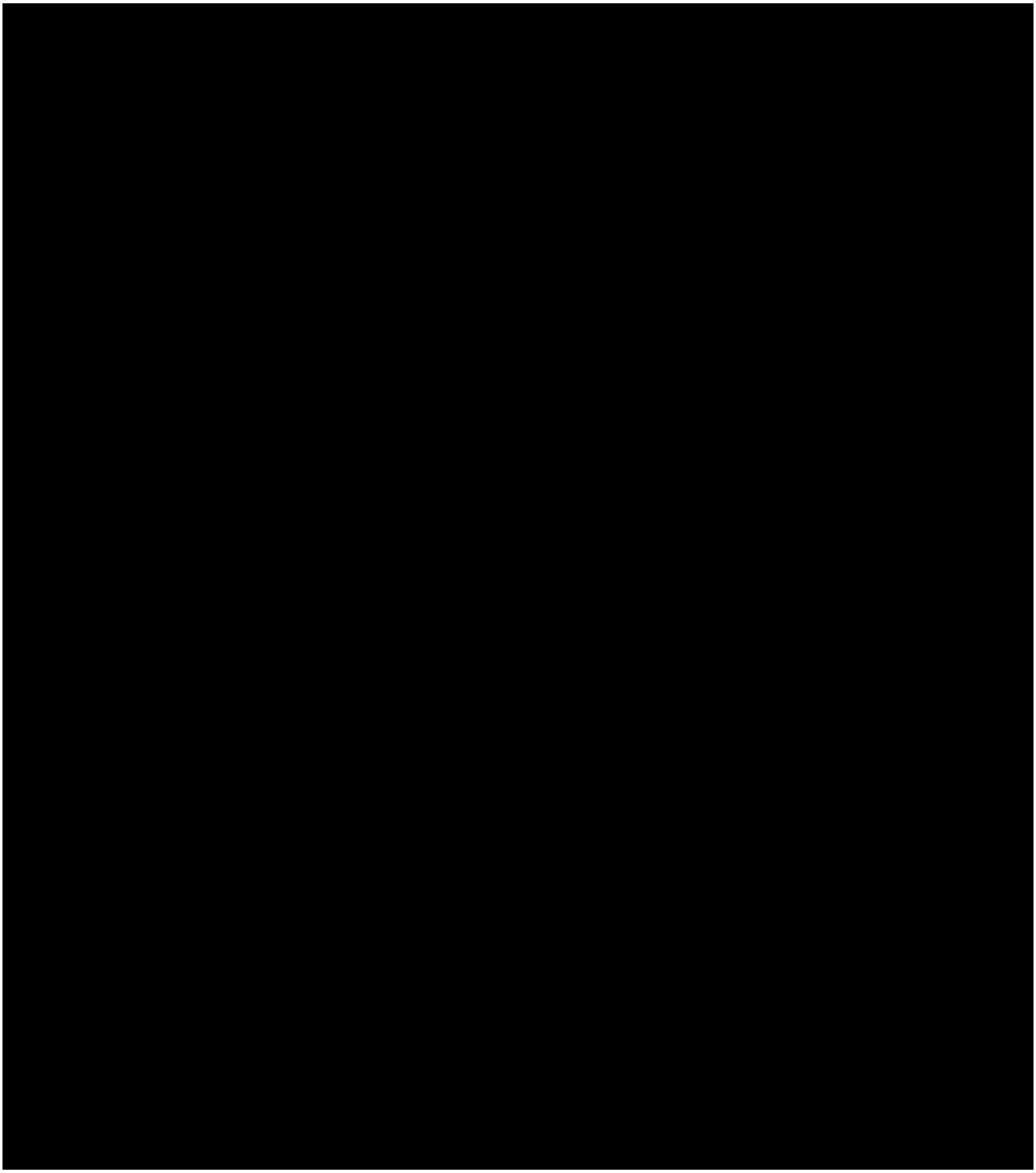
Table 2-2 Criteria for Clinically Notable Vital Sign Abnormalities

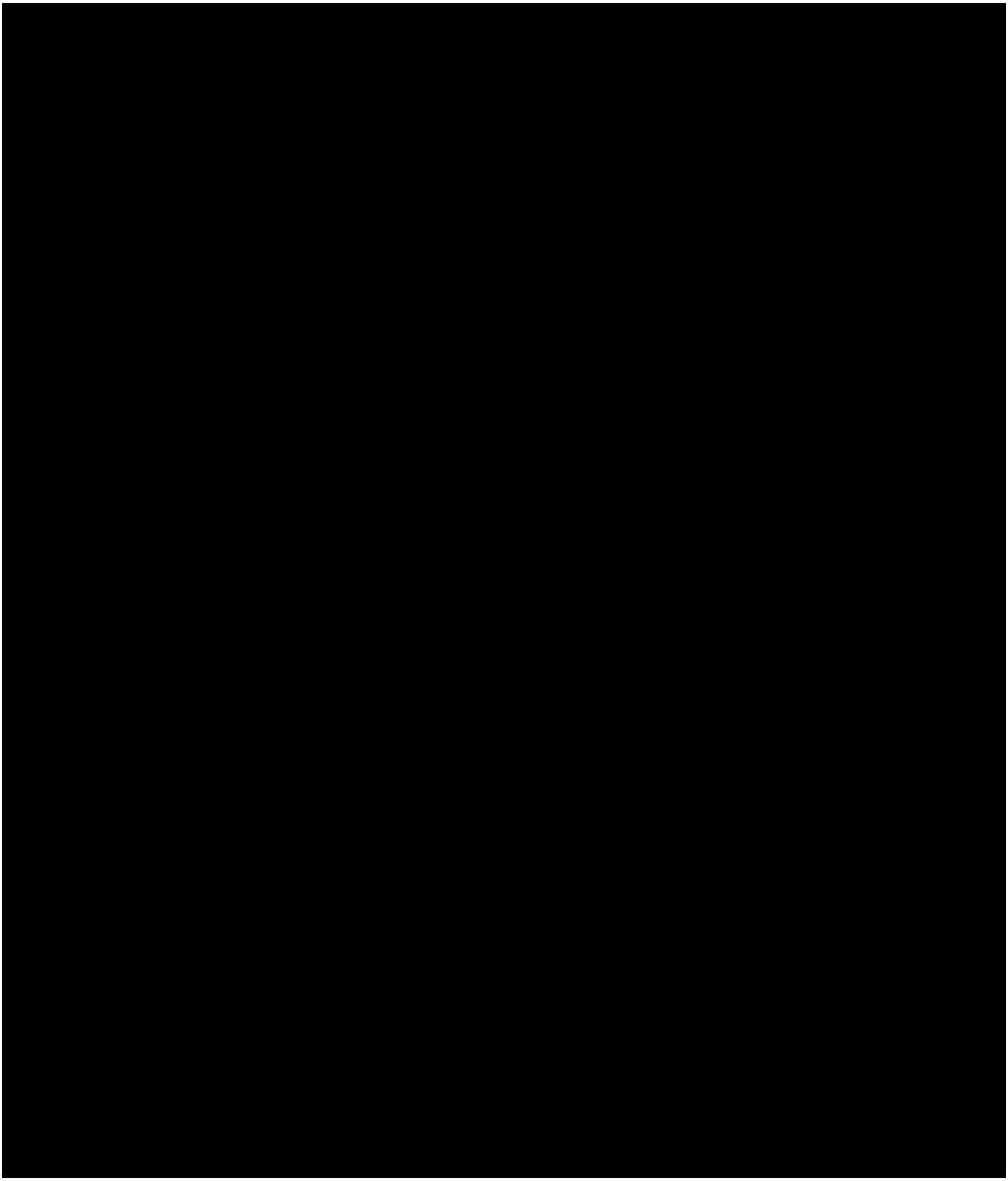
Parameter	High Threshold	Low Threshold
Systolic Blood Pressure	>160 mm Hg	<85 mm Hg
Diastolic Blood Pressure	>95 mm Hg	<50 mm Hg
Respiratory rate	>24 per minute	<8 per minute
Temperature	≥37.5°C	≤35.0°C
Sitting pulse	≥120 bpm	≤50 bpm

All vital signs will be listed with updated data for the final analysis.

2.11 Patient-reported outcomes

Outputs of all EORTC QLQ-C30 and summary of Seven-day modified MFSAF questionnaires were reported in “the Week 24 CSR” and not applicable in this document. The Change in total symptom score by Seven-day modified MF-SAF v2.0 questionnaire will be summarized and listed with updated data for the final analysis.





2.14 Interim analysis

A single interim analysis was conducted by the Novartis statistician.

With regard to detailed plan for the interim analysis, please refer to Section 4.9 in "CINC424A2202 RAP Module 3 Detailed statistical methodology Amendment 2".

3 Sample size calculation

The planned sample size of 110 was determined based on the single-sample binomial test (normal approximation).

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 ≥ 35% reduction in spleen volume from Baseline at 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 a response rate of 0.7% was observed in the placebo group.

Based on the results obtained in Study INCB 18424-351, the proportion of patients on this study achieving ≥35% reduction in spleen volume from Baseline at 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 the 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 (i.e., 2-stage) design accruing 110 total patients with the same final time-point boundary (≥ 31/110) and an interim analysis conducted after 50 patients using an O'Brien-Fleming type interim analysis boundary (≥ 19/50) is approximately 0.95. Therefore, the effect of the interim analysis on the overall study power is negligible.

4 Change to protocol specified analyses

Not applicable.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Concomitant medication (CMD) imputation rules in Section 5.1.3 will be applied for AE date imputation.

5.1.3 Concomitant medication date imputation

The following Table 5-1 explains the notation used in the logic matrix. Please note that, if the date is completely missing, it will not be imputed.

Table 5-1 CMD/ treatment date abbreviations

	Day	Month	Year
Partial CMD Start Date	Not used	MON	YYYY
Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix Table 5-2 describes the possible combinations and their associated imputations. In the boxes the upper text indicates the imputation and the lower text indicates the relationship of the CMD start date to the treatment start date (TRTSTD).

Table 5-2 CMD partial date imputation algorithm

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(C) Uncertain	(C) Uncertain	(C) Uncertain	(C) Uncertain
YYYY < TRTY	(D) Before TRTSTD	(A) Before TRTSTD	(A) Before TRTSTD	(A) Before TRTSTD
YYYY = TRTY	(C) Uncertain	(A) Before TRTSTD	(C) Uncertain	(B) After TRTSTD
YYYY > TRTY	(E) After TRTSTD	(B) After TRTSTD	(B) After TRTSTD	(B) After TRTSTD

The following Table 5-3 is the legend to the above table.

Table 5-3 CMD/treatment date relationship and imputation legend

Relationship	
Before TRTSTD	Partial date indicates CMD start date prior to Treatment Start Date
After TRTSTD	Partial date indicates CMD start date after Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of CMD start date to Treatment Start Date
Imputation calculation	
(A)	15MONYYYY
(B)	MAX(01MONYYYY, TRTSTD+1)
(C)	TRTSTD+1
(D)	01JULYYYY
(E)	01JANYYYY

5.1.3.1 Prior therapies date imputation

CMD imputation rules in Section 5.1.3 will be applied for prior therapies imputation with exception that for scenario (B) will be replaced to be 'Treatment Start Date (TRTSTD) - 1'.

5.1.3.2 Post therapies date imputation

CMD imputation rules in Section 5.1.3 will be applied for post therapies imputation.

5.1.3.3 Other imputations

Not applicable.

5.2 AEs coding/grading

Adverse events are coded using the Medical dictionary for regulatory activities (MedDRA) terminology. MedDRA version in effect prior to database lock will be used for CSR AE reporting.

AEs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

5.3 Laboratory parameters derivations

CTC grading for blood differentials is based on absolute values. However, this data may not be reported as absolute counts but rather as percentage of WBC.

If laboratory values are provided as '<X' (i.e. below limit of detection) or '>X', prior to conversion of laboratory values to SI unit, these numeric values are set to X.

The following rules will be applied to derive the WBC differential counts when only percentages are available for a xxx differential

xxx count = (WBC count) * (xxx %value / 100)

Further derivation of laboratory parameters might be required for CTCAE grading. For instance, corrected calcium can be derived using the reported total calcium value and albumin at the same assessment using the following formula:

Corrected Calcium (mg/dL) = Calcium (mg/dL) – 0.8 [Albumin (g/dL)-4]

In order to apply the above formula, albumin values in g/L will be converted to g/dL by multiplying by 0.1), calcium values in mmol/L will be converted to mg/dL by dividing by 0.2495. For calculation of laboratory CTC grades 0 and 1, the normal range for derived corrected calcium is set to the same limits (in mg/dL) as for calcium.

CTC grades for the derived absolute WBC differential counts (neutrophils, lymphocytes) and corrected calcium will be assigned as described above for grading.

In order to derive the corresponding absolute normal range, the rule to be applied depends on the availability of the % range and the absolute range for the differential:

- If absolute range is NOT missing (% range is or is not missing), then use the absolute range provided by the site.
- If % range is NOT missing and absolute range is missing, then the % normal limits (i.e., LLN and ULN) are divided by 100 and multiplied by the corresponding normal limits of WBC count, e.g., for neutrophils (NEU):

  LLN for NEU count = (LLN for WBC count) x (LLN for NEU%value / 100),

  ULN for NEU count = (ULN for WBC count) x (ULN for NEU%value / 100)

5.4 Statistical models

5.4.1 Primary analysis

Not applicable.

5.4.2 Key secondary analysis

Not applicable.

5.5 Rule of exclusion criteria of analysis sets

All non-minor protocol deviations (any PD leading to exclusion from any analysis data set) are given in Table 5-4. The complete list of protocol deviations is given in VAP module 3 (Protocol Deviations).

Table 5-4 Major protocol deviations

Deviation code	Text description	Severity code
I02	Unconfirmed diagnosis of PMF, PPV-MF or PET-MF	0
I03	Patient without a palpable spleen >= 5 cm	1
I04	Patient without 2 or more risk factors	1
I10	Patient had previous therapy with a JAK2 inhibitor	1
E07	Patient had splenic irradiation within 12 months prior to screening	1
E09	Patient being treated with another investigational drug not intended for MF or having been treated with such a drug within 14 days prior to Baseline or 6-half lives of the drug, whichever is longer	1
E16	Patient is unable to comprehend or is unwilling to sign the ICF	8
[redacted]		
C01	Patient with no post-baseline safety assessments	5
C02	Patient with no post-baseline spleen volume assessment	1
M03	Use of any investigational medication other than INC424 during the study	2
M04	Use of any other drugs for MF including hydroxyurea, interferon, thalidomide, busulfan, lenalidomide or anagrelide during the study	2
M05	Use of potent CYP3A4 inducers	20

Table 5-5 shows the subject classification based on the severity code for each analysis population.

Table 5-5 Subject classification

	Severity code					
Population	**0**	**1**	**2**	**5**	**8**	**20**
FAS	No	Yes	Yes*	Yes	No	Yes
PPS	No	No	Yes*	Yes	No	Yes
SAF	Yes	Yes	Yes*	No	No	Yes
PAS	No	Yes	Yes*	Yes	No	No

Note: 'Yes' means inclusion in the analysis set, 'No' means exclusion from the analysis set.

* means that partial data post-deviated date will NOT be used for any analyses.

6 Reference

- Cervantes F, Dupriez B, Peteira A, et al. (2009) New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood; 113:2895-901.