NOVARTIS

Clinical Development

Ruxolitinib / JAKAVI (INC424)

CINC424A2201 (EXPAND)

A Phase Ib, open-label, dose-finding study of the JAK inhibitor INC424 tablets administered orally to patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV-MF) or Post-Essential Thrombocythemia-Myelofibrosis (PET-MF) and baseline platelet counts ≥ 50 $x10^9$/L and <100 $x10^9$/L

RAP Module 3 – Detailed Statistical Methodology Amendment 2

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Document History – Changes compared to previous version of RAP module 3.

Version	Date	Changes
1.0	27 Nov2017	1) List of Abbreviations: added LPFV, last patient first visit. 2) In section 1.2, updated treatment duration to reflect that UK patients may continue on study treatment past Week 156 and until LPFV plus 156 weeks. 3) In section 1.2 & 2.7 and figure 1-1, updated study design to reflect the new dose for Stratum 1 as 10 mg BID and to reflect the requirement to enroll approximately 20 patients at this dose, or enroll the last patient by 01 Sept 2017, whichever comes first. 4) In section 2.1.1 & 2.1.3, the grouping scheme was updated. 5) In section 2.3.2, version of MedDRA was updated. 6) In section 2.1.1 the second condition of the definition of the Dose Determining Set (DDS) was updated from “all patients from the Safety Set who (ii) discontinue due to DLT” to “all patients from the Safety Set who (ii) experience a DLT” to ensure all patients experiencing a DLT are included in the DDS regardless of whether they permanently discontinued treatment as Protocol Section 5.1.2.8 defines circumstances where patients who have experienced a DLT can resume treatment.
2.0	20 Jan2020	1) Section 2.2.2: Study treatment groups were updated to depict TFLs 2) Section 2.2.3: Clarification was added that the concomitant medication reported after the 30 days will be flagged in the listing. 3) Section 2.3.2: Post treatment deaths were added and clarifications that additional safety outputs might be provided to cover RMP commitment. 4)Section 2.3.3.: Clarification on the lab output was provided 5) Section 2.3.4: To delete presentation on Physical examination and antineoplastic medication, because these data were not collected on the CRF.

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List of abbreviations

AE	Adverse Event
ANC	Absolute Neutrophil Count
BLRM	Bayesian Logistic Regression Model
BMI	Body Mass Index
bpm	Beats per minute
CRF	Case Report/Record Form
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTT	Clinical Trial Team
DDS	Dose-Determining Set
DI	Dose Intensity
DLT	Dose Limiting Toxicities
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EWOC	Escalation With Overdose Control
eCRF	Electronic Case Report Form
[redacted]	[redacted]
FAS	Full Analysis Set
IWG	International Working Group
[redacted]	[redacted]
LPFV	Last Patient First Visit
[redacted]	[redacted]
MF	Myelofibrosis
[redacted]	[redacted]
MSSD	Maximal Safe Starting Dose
PET-MF	Post Essential Thrombocythemia-Myelofibrosis
PD	Pharmacodynamic
PK	Pharmacokinetic
PLT	Platelet
PMF	Primary Myelofibrosis
PPV-MF	Post Polycythemia Vera-Myelofibrosis
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
RAP	Report and Analysis Plan
SAE	Serious Adverse Event
SEC	Safety Event Categories
SMQ	Standard MedDRA Query
WHO	World Health Organization

1 Introduction

This RAP module describes the planned statistical methods for all safety and efficacy analyses as per Protocol Amendment 4.

1.1 Study objectives

Primary

- To establish the Maximal Safe Starting Dose (MSSD) of INC424 in patients with Myelofibrosis (MF) and baseline Platelet (PLT) count $< 100 \times 10^9$/L and $\geq 75 \times 10^9$/L (Stratum 1) and PLT count $< 75 \times 10^9$/L and $\geq 50 \times 10^9$/L (Stratum 2)

Secondary

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

Exploratory

[redacted]

1.2 Study design

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

For each patient, the study consists of 2 periods:

1. The core study period [first 168 days of study]
2. The extension period [beyond Study Day 168 visit] until 3 years as per Protocol Amendment 3 [as per Protocol Amendment 4, for patients in the United Kingdom only: After 3 years of study treatment, if the patient continues to benefit in the opinion of the Investigator and does not have access to study drug outside of this clinical trial, the patient may continue on study treatment until LPFV plus 3 years. After LPFV plus 3 years, if the study treatment is not commercially available and reimbursable in the UK, an alternative UK-specific free of

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

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

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

As per Protocol Amendment 3, after the initial 24 weeks of core treatment period from Study Day 1 to Study Day 168, patients will enter the extension treatment period from Study Day 168 (Week 24) until 3 years (Week 156) [as per Protocol Amendment 4, except in the UK, which is up to LPFV + 156 weeks]. In the extension period, safety and efficacy parameter of spleen length will be collected with reduced frequency.

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

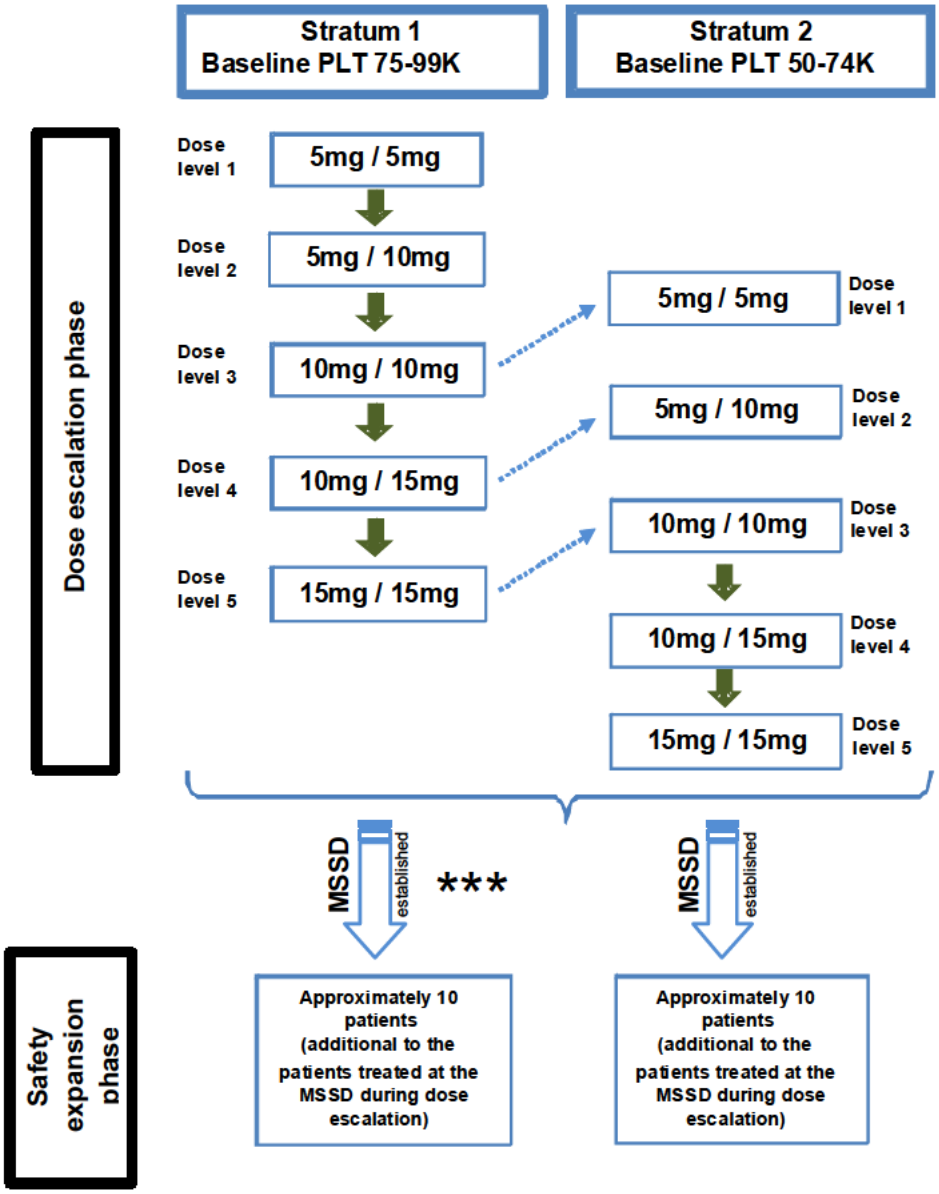
Following determination of the MSSD, a safety expansion phase will be conducted. Patients from both strata can be enrolled simultaneously during the safety expansion phase, allocated to a dose equal to the respective MSSD for their stratum. If the MSSD is the same in both strata, all patients in the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

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

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

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

Figure 1-1 Study design



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

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

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

*** As of Amendment 4, new patients enrolled to Stratum 1's safety expansion phase will be given the 10 mg BID dose, instead of the 15 mg BID dose level previously evaluated as the MSSD. Approximately 20 patients will be evaluated at this dose level in Stratum 1, inclusive of the patients already enrolled into this dose during the dose escalation phase.

2 Statistical and analytical plans

Data will be analyzed according to the data analysis section 9 of the study protocol which is available in Appendix 16.1.1 of the CSR.

In the CSR, we will summarize all data from each patient, without separating the core study period and the extension period.

The corresponding primary analysis method is an adaptive Bayesian logistic regression model (BLRM) guided by escalation with overdose control (EWOC) (Babb et al 1998). A prior distribution for the model parameters is derived based on experience with INC424 in adult patients in clinical study INCB 18424-251, which was the dose-finding study in patients with myelofibrosis that preceded the pivotal phase III studies. This prior distribution is then updated after each cohort of patients in each stratum with the DLT data from the current study. Description of the prior elicitation can be found in the study protocol. More details on presentation of final BLRM model are given later in the safety section.

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

All data will be listed unless otherwise specified.

2.1 Definitions for subjects and treatments

2.1.1 Analysis sets

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

Safety Set includes all patients who received at least one dose of study medication.

Note that the patient population for both FAS and Safety Set are the same.

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

Note: this is a clarification to the definition of the DDS in Section 9.1.3 of the protocol. The DDS contains all patients who experienced a DLT regardless of whether they permanently discontinued treatment as Section 5.1.2.8 defines circumstances where patients who experienced a DLT can resume treatment.

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

Patients in the DDS will be identified based on the list of evaluable patients used for determination of the MSSD, as well as the VAP M3 Protocol Deviations. Patients with protocol deviation code 18 (indicating exclusion from dose-finding population) will be excluded from DDS.

Patients will be analyzed by stratum and for each stratum, patients will be categorized according to the first dose level they received. Patients will be categorized the following way: (1) Group 1, including patients with starting dose of 5mg AM + 5mg PM or 5mg AM + 10mg PM; (2) Group 2, including patients with starting dose of 10mg AM + 10mg PM; (3) Group 3, including patients with starting dose of 10mg AM + 15mg PM or 15mg AM + 15mg PM. Such categorization depends on the highest dose level being reached in each stratum. For example, the highest dose level reached in Stratum 2 is 10mg AM + 10mg PM, so there will be only two groups for Stratum 2: (1) Group 1, including patients with starting dose of 5mg AM + 5mg PM or 5mg AM + 10mg PM; (2) Group 2, including patients with starting dose of 10mg AM + 10mg PM.

2.1.2 Study day

The study day is calculated as:

For assessments starting on or after the start date of study treatment:

Study day = date of examination – start date of study drug + 1.

For assessments starting before the start date of study treatment:

Study day = date of examination – start date of study drug.

2.1.3 Treatments

During the study all patients will receive INC424 tablets. INC424 tablets will be the only investigational drug in this study.

The following notation will be used for the dose levels by stratum:

Daily dose regimens Morning dose + evening dose		Dose levels	Dose levels for stratum 1	Dose levels for stratum 2	Reporting for stratum 1	Reporting for stratum 2
5mg AM	+ 5mg PM	1	S1D1	S2D1	Group 1	Group 1
5mg AM	+ 10mg PM	2	S1D2	S2D2	Group 1	Group 1
10mg AM	+ 10mg PM	3	S1D3	S2D3	Group 2	Group 2
10mg AM	+ 15mg PM	4	S1D4	S2D4	Group 3	Group 3
15mg AM	+ 15mg PM	5	S1D5	S2D5	Group 3	Group 3

Baseline for efficacy and safety assessments is defined as last assessment prior to or on the first INC dose date unless there is a separate definition provided [redacted].

2.2 Subjects and treatments

2.2.1 Demographics and other baseline characteristics

Demographic characteristics will include age, age group (<65, >=65), sex, race, ethnicity, Body Mass Index (BMI) and Eastern Cooperative Oncology Group (ECOG) status at baseline. BMI [kg/m2] = weight[kg] / (height[m]**2). Ethnicity will be presented as three categories: Hispanic or Latino; Not Hispanic or Latino; Missing.

Disease history and characteristics will include type of myelofibrosis, time since diagnosis, IWG risk level at screening, prior use of hydroxyurea, prior use MF medication, prior splenic radiotherapy, [redacted], palpable spleen size below costal margin, [redacted], qualifying platelet count, last pre-dose (baseline) platelet count, baseline hemoglobin, and baseline Absolute Neutrophil Count (ANC). Qualifying platelet baseline count is defined as the platelet count at any 4 assessments (at screening, at screening re-test, at the planned day of first study treatment or at its re-test) within qualifying interval for a stratum, i.e. for stratum 1, qualifying platelet count is the last assessment prior to or on the first INC dose date within [75 - 100) x 10^9 / L, for stratum 2 is the last assessment prior to or on the first INC dose date within [50 - 75) x 10^9 / L.

Demographics and other baseline data will be summarized descriptively by stratum and by group for the FAS.

Relevant medical history will be summarized by SOC and PT by stratum and by dose for the FAS

2.2.2 Study treatment

Study treatment data will be summarized descriptively by stratum and group using the Safety Set.

The duration of exposure will be summarized by length of exposure, as well as by duration category (none, < 4 weeks, 4 – < 8 weeks, 8 – < 12 weeks, 12 – < 16 weeks, 16 – < 20 weeks, 20 – < 24 weeks, 24 – < 36 weeks, 36 – < 48 weeks, 48 – < 60 weeks ect).

The following algorithm will be used to calculate the duration of study treatment exposure.

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

The duration includes the periods of temporary interruption.

Study dose

Cumulative dose is defined as the total dose given during the study treatment exposure. For patients who did not take any drug, the cumulative dose is by definition equal to zero. The total dose taken will be calculated based on INC424 DOSE eCRF page. Dose intensity (DI) is defined as:

$$\text{DI (mg/day)} = \text{Cumulative dose (mg)} / \text{Duration of exposure (days)}$$

Relative dose intensity (RDI) for the first cycle of treatment is defined as:

$$\text{RDI (\%)} = (\text{Cumulative dose over first cycle}) / (\text{Total planned starting dose over first cycle}) \times 100\%$$

where total planned starting dose as Duration of treatment (days) * starting dose of the assigned cohort.

The summaries of cumulative dose, DI and RDI will be presented.

A dose reduction is defined as a reduction of the total daily dose to a non-zero dose of one day or greater. A dose interruption is defined as a total daily dose of 0 mg for a duration of one day or greater.

The number (%) of subjects who had a dose interruption or dose reduction will also be summarized.

The dosing information will be listed by stratum, dose level and patient.

2.2.3 Concomitant therapy

The start/stop dates recorded in the electronic case report form (eCRF) will be used to identify when a concomitant medication or a significant non-drug therapy was taken during the study.

Concomitant medications and significant non-drug therapies after the start of the study treatment will be listed and summarized by ATC class and standardized medication term for the Safety Set. These summaries will include medications starting on or after the start of study treatment or medications starting prior to the start of study treatment and continuing after the start of study treatment. Any prior medications and significant non-drug therapies starting and ending prior to the start of study treatment will be listed. These analyses will be based on Safety Set.

Results of concomitant medications and significant non-drugs medications will be listed. Records after 30 days of end of treatment period will be flagged.

Any missing start date will be queried for resolution. For any unsolved missing start dates, the following rules in the following order will be applied to decide if a concomitant medication or a significant non-drug therapy was taken after the start of the study treatment and to decide if the data should be included in the summary table. Originally collected start date will be listed in listings.

- If the date is completely missing, the Day 1 date will be used as the missing start date.
- If only the day is missing, and the last day of the month is prior to Study Day 1, the concomitant medication will be then considered as starting prior to Day 1.
- If only the day is missing, and the 1st day of the month is after the 1st dosing date on Day 1, the concomitant medication will then be considered as starting after Day 1.
- If only the day is missing, and the month is equal to the month of the 1st dosing date on Day 1, Study Day 2 will be used as the missing day.
- If both the month and day are missing, and the last day of the year is prior to Study Day 1, the concomitant medication will then be considered as starting prior to Day 1.

No rule will be applied to any missing stop date. If *Start/Stop* will be the start/stop date of a concomitant medication, *Date1* will be the date of first INC dose, the concomitant medication will then be allocated to 1 or more summary groups according to the following algorithm as shown in Table 2-1.

Table 2-1 Allocation of concomitant medications

If	Prior Medication	Treatment Phase
Stop≤Date1	X	
Start≤Date1 and Stop=missing and ongoing	X	X
Start<=Date1<=Stop	X	X
Start>Date1		X

2.2.4 Prior medications to treat MF

Prior medications to treat MF will be summarized. The information will include drug name, start and stop dates, best response to therapy, and reasons for discontinuations. This information will be summarized by World Health Organization (WHO) drug class (ATC class) and WHO drug term (the most recent version available), and will be listed by subject, age, sex, MF type, MF therapy name, start and stop dates, and best response.

2.2.5 Compliance

Compliance to the study protocol will be assessed by reporting the number and type of CSR reportable protocol deviations. These will be identified in the VAP document for Protocol Deviation prior to database lock and will be listed and summarized. Compliance to study drug, for the period from Study Day 1 to end of first cycle, i.e. RDI for the first cycle of treatment will be summarized by categories of < 83.3% vs. ≥ 83.3% and will be reported by dose level.

2.3 Safety evaluation

For all safety analyses, the Safety Set will be used, except for summaries of DLTs, which will be presented for the DDS. All listings will be presented by dose levels and all tables will be presented by groups of dose levels in the Safety Set.

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

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

2.3.1 Bayesian logistic regression model

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

The corresponding primary analysis method is an adaptive Bayesian logistic regression model guided by escalation with overdose control (EWOC). A prior distribution for the model parameters is derived based on experience with INC424 in adult patients in clinical study [INCB

18424-251], which was the dose-finding study in patients with myelofibrosis that preceded the pivotal phase III studies [INC424A-351] and [INC424A-352]. This prior distribution is then updated after each cohort of patients in each stratum with the DLT data from the current study.

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

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

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

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

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

Following the principle of dose-escalation with overdose control (EWOC), after each cohort of patients the recommended dose is the one with the highest posterior probability of DLT in the target interval [16%, 33%) among the doses fulfilling the overdose criteria, namely that there is less than 25% chance that the true rate of DLT falls in the excessive toxicity interval. The dose recommended by the adaptive BLRM for each stratum may be regarded as information to be integrated with a clinical assessment of the toxicity profiles observed thus far in determining the next dose to be investigated.

Once the MSSD is established for both strata the BLRM will be updated with DLT information and a table with posterior probabilities of DLT for different doses by stratum will be included in the study report.

2.3.2 Adverse Events (AE)

AEs will be summarized using the most recent medical Dictionary for Regulatory Activities (MedDRA) terminology version available.

DLT summaries

DLTs will be listed and their incidences summarized by primary system organ class, worst grade, type, and dose level. The DDS will be used for these summaries. Criteria for defining DLT are listed in protocol Table 5-3. The following summaries will be produced for patients in the Safety Set with number (%) of patients:

- reporting dose-limiting toxicities within first 28 days of treatment, by system organ class and preferred term.

AE summaries

Summary tables for adverse events (AEs) have to include only AEs that started or worsened during the on-treatment period, the ***treatment-emergent*** AEs. However, all safety data (including those from the post-treatment period) will be listed and those collected during the pre-treatment and after 30 days of post- treatment period are to be flagged.

Any missing onset date, causality, or severity must be queried for resolution. Unsolved missing values will be imputed according to the following:

- An unsolved missing causality will be left as missing.
- An unsolved missing severity will be left as missing in the AE tables. For AEs listed by highest severity, AE terms with missing severity will be excluded.
- An unsolved missing onset date will be imputed by the date of **Day 2**, which will force the AE to be treatment emergent, with the following exceptions:
  - If the stop/resolution date is prior to Study Day 1, the AE will then be considered as not being treatment-emergent.
  - If both the month and day of the onset date are missing, and the last day of the year is prior to Study Day 1, the AE will then be considered as not being treatment-emergent.
  - If only the day of the onset date is missing, and the last day of the month is prior to Study Day 1, then the AE will be considered as not being treatment-emergent.
  - If only the day of the onset date is missing, and the 1st day of the month is after Study Day 1, the AE will then be considered as being treatment-emergent, and the incomplete date will be imputed as the 1st of the month.
  - If the non-missing stop/resolution date is equal to Study Day 1, the AE will then be considered as not being treatment-emergent.

Specific safety event categories (SEC) include groups of reported adverse events of high interest as outlined in the product case retrieval sheet. The version of the most up to date document used for the clinical study report will be provided in tables footnotes.

For each specified SEC, number and percentage of patients with at least one event part of the SEC will be reported.

One summary table will be produced for AE to summarize the number (%) of patient from Safety Set:

- who died.
- who died during study treatment and within 30 days after discontinuation of study treatment.
- Who died after 30 days from treatment discontinuation
- reporting AEs regardless of relationship to study treatment.
- reporting AEs with suspected relationship to study treatment.
- reporting SAEs regardless of relationship to study treatment.
- reporting SAEs with suspected relationship to study treatment.

- reporting AEs of CTC grade 3-4 regardless of relationship to study treatment.
- who discontinued from study due to AEs.
- AEs requiring study drug dose adjustment or interruption
- reporting AEs of specific safety event categories. The list of categories will be based on the latest version of case retrieval sheet.

The following summaries will be produced for patients in the Safety Set with number (%) of patients:

- reporting AEs, regardless of relationship to study drug, by system organ class and preferred term.
- reporting AEs, regardless of relationship to study drug, by preferred term.
- reporting AEs, for patients who died, by system organ class and preferred term.
- reporting SAEs, regardless of relationship to study drug, by system organ class and preferred term.
- reporting AEs leading to discontinuation, regardless of relationship to study drug, by system organ class and preferred term.
- reporting AEs requiring dose adjustment or study-drug interruption, regardless of relationship to study drug, by system organ class and preferred term.
- reporting specific safety event categories (SEC), regardless of relationship to study drug, by SEC category.
- reporting AEs, with suspected relationship to study drug, by system organ class and preferred term.
- reporting SAEs, with suspected relationship to study drug, by system organ class and preferred term.
- reporting AEs leading to discontinuation, with suspected relationship to study drug, by system organ class and preferred term.
- reporting AEs requiring dose adjustment or study-drug interruption, with suspected relationship to study drug, by system organ class and preferred term.
- reporting AEs, but not SAEs, regardless of relationship to study drug, by system organ class and preferred term .

Additional outputs to cover RMP comitments may be added in this analsysis.

2.3.3 Laboratory abnormalities

For laboratory tests covered by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NCI 2009). A grade 0 will be assigned for all non-missing values not graded as 1 or higher. Grade 5 will not be used. All lab values occurring between the treatment start date and 30 days after the end of the study treatment will be taken into account.

The following by-strata summaries will be generated separately for hematology, coagulation and biochemistry laboratory tests:

- frequency table for newly occurring or worsened on-treatment abnormalities
- 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.

A summary and a plot will be produced for hemoglobin level and platelet count over time by visit and stratum.

2.3.4 Other safety data

Vital signs

The following thresholds will be used for the notable abnormal vital signs

Table 3-2 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
Pulse Rate	> 100 bpm	< 50 bpm
Respiratory Rate	> 24 per minute	< 8 per minute
Body temperature	>38°C	<35.5°C

bpm = beats per minute

The number and percent of subjects with notably abnormal vital signs, defined as the absolute value being out of the above defined range, will be summarized by treatment group.

A summary table will be produced for incidence of notably abnormal vital sign abnormalities, i.e. shift table from baseline to worst on-treatment result.

A summary table will be produced with descriptive statistics at baseline, worst post-baseline and change from baseline to the worst post-baseline.

ECG

The following analysis will be done for ECG data

- Shift table baseline to worst on-treatment result for overall assessments
- Listing of ECG evaluations for all patients will also present any abnormality

2.4 Pharmacokinetic evaluations (PK, PK/PD)

The pharmacokinetics will be evaluated by population pharmacokinetic modeling methods in a separate report. The analysis plan of this report and conduct of the analysis will be done by Incyte.

2.4.1 Pharmacokinetic-Pharmacodynamic data analysis

Relationships between the pharmacokinetic model predicted concentration/PK parameters and PD and safety/efficacy parameters were planned. All these as well as cytokines (if analysis

permitted) and depending on the quality of data available, may be reported in the a separate report Efficacy evaluation

Efficacy is a secondary endpoint in this study.

Change in spleen length below left costal margin

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

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

The percentage change in spleen length is defined as:

% Change = (Post-baseline spleen length – Baseline spleen length) ×100 / Baseline spleen length.

A waterfall plot will be produced for best response in spleen length by stratum. Best response is defined as the minimum value in non-missing percent change from baseline.

Spleen length measurement with absolute and percent change from baseline will be summarized by time and by stratum.

For Interim Analysis, the current protocol time windows as specified in the latest protocol amendment Tables 6-3, 6-4, 6-5, 6-6 will be used for all visit based assessments.

2.5 Exploratory objectives

[redacted]

[redacted]

[redacted]

[redacted]

2.6 Determination of sample size

Cohorts of at least 3 patients per dose level and stratum will be enrolled from the DDS including at least 9 patients at the MSSD level within each stratum from the DDS. Due to the potential for dropouts during the first treatment cycle (e.g. early disease progression), a cohort may be expanded to include additional patient(s). Cohorts may be expanded at any dose level below the MSSD for further elaboration of safety and pharmacokinetic parameters if deemed appropriate per the CTT. Approximately 21 patients are planned within each stratum in the dose-finding portion of the study assuming 3 patients treated at each dose level and 5 dose levels tested. Once the MSSD is determined, an additional 10 patients will be enrolled per stratum in the safety expansion phase in order to further evaluate the endpoints on patients starting at the MSSD.

Based on a review of the interim analysis data, a decision was made to expand the 10 mg BID starting dose for Stratum 1. Following the approval of Amendment 4, new patients enrolled to Stratum 1's safety expansion phase will begin treatment with ruxolitinib at 10 mg BID. In line with the original sample size specification for the MSSD cohorts (i.e. $\geq$ 9 patients for dose escalation phase and 10 patients for safety expansion phase), approximately 20 patients in total will be enrolled, including those already enrolled at the 10 mg BID dose level in Stratum 1.

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

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

Clinical Study Report - Appendix 16.1.9 Documentation of statistical methods

[redacted]