NOVARTIS

Clinical Development

INC424 / Ruxolitinib / JAKAVI®

CINC424A2353 / NCT02598297

# A randomized, double blind, placebo-controlled, multi-center, Phase III study investigating the efficacy and safety of ruxolitinib in Early Myelofibrosis patients with high molecular risk mutations

Statistical Analysis Plan (SAP) – Amendment 1

**TEMPLATE VERSION AND DATE: Final 1.0 24-Sep-2015, Effective 31-Oct-2015**

Author: [redacted]

Document type: SAP Documentation

Document status: Final 1.0

Release date: 25-July-2017

Number of pages: 30

## Document History – Changes compared to previous final version of SAP

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| 29-Jan-2016 | Prior to DB lock | Creation of final version | N/A - First version | NA |
| 19-Jul-2017 | Prior to DB lock | Creation of amendment 1 due to study premature termination | Change to the ultimate goal of the early termination study: To present the efficacy, safety and [redacted] data of interest. | Introduction section 1.2 |
| | | | Specified that primary endpoint PFS, and other time to event endpoints will not be derived. | Introduction section 1.2 |
| | | | Removed Per-Protocol Set and PK Set, and Subgroup of interest. | Analysis sets Section 2.2 |
| | | | Treatment period 1 data will be tabulated, Treatment period 1 and period 2 data will be listed. | Sections 2.3, 2.4, 2.5, 2.7, 2.8 |
| | | | Specified that no analysis for primary endpoint is planned. The early terminated study aims to present data collected for the endpoints of interest, including change in spleen volume and length from baseline, change in symptoms using MF-7 and EQ-5D from baseline (see patient reported outcomes section), safety endpoints, [redacted] Descriptive statistics will be used to summarize the endpoints of interest and the FAS will be used for analyzing the data. | Analysis of the primary objective section 2.5 |
| | | | Specified that no sufficient data were collected to assess the effect of ruxolitinib versus placebo on overall survival and time to progression, so that no secondary | Analysis of the secondary objectives section 2.7 |

| Date | Time point | Reason for update | Outcome for update | Section and title impacted (Current) |
|---|---|---|---|---|
| | | | efficacy analysis will be performed in this study. | |
| | | | AESI is not planned for this prematurely terminated study. | Section 2.8.1.1 |
| | | | Add text to AE of clinical trial safety disclosure. | Section 2.8.1.2 |
| | | | No formal PK analysis is planned. Individual plasma ruxolitinib concentration data will only be listed for the Full analysis set. | PK Section 2.9 |
| | | | [redacted] | |

## Table of contents

## List of abbreviations

| | |
|---|---|
| AE | Adverse event |
| ATC | Anatomical Therapeutic Classification |
| AUC | Area Under the Curve |
| bid | bis in diem/twice a day |
| CSR | Clinical Study Report |
| CTC | Common Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DMC | Data Monitoring Committee |
| FAS | Full Analysis Set |
| eCRF | Electronic Case Report Form |
| IRT | Interactive Response Technology that includes Interactive Voice Response System and Interactive Web Response System |
| MedDRA | Medical Dictionary for Drug Regulatory Affairs |
| NCI | National Cancer Institute |
| o.d. | Once Daily |
| OS | Overall Survival |
| PFS | Progression-Free Survival |
| PK | Pharmacokinetics |
| PPS | Per-Protocol Set |
| PRO | Patient-reported Outcomes |
| qd | Qua'que di'e / once a day |
| QoL | Quality of Life |
| RAP | Report and Analysis Process |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| TFLs | Tables, Figures, Listings |
| WHO | World Health Organization |

# 1 Introduction

The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of the statistical analysis planned in the protocol for the abbreviated clinical study report (CSR) and potential publications.

The study is terminated prematurely due to unresolvable recruitment issues. Descriptive statistics and listings of safety, efficacy and biomarker data of interest is planned for reporting CINC424A2353. No formal statistical analyses for progression free survival (PFS) are planned as the number of patients enrolled in the study is insufficient to perform confirmative analysis.

The latest MedDRA version by the time of DBL should be used for the CSR.

## 1.1 Study design

This is a double blind, randomized placebo-controlled study of ruxolitinib in patients with HMR positive early MF (HMR+ EMF). The study consists of a screening period, Treatment Period 1 and Treatment Period 2.

Details of the discontinuation from study/treatment, unblinding, planning of the EOT assessment and safety monitoring are documented in the Premature Termination Plan.

### Screening:

Patients will be pre-screened for the determination of HMR mutation status after obtaining the molecular pre-screening informed consent. Only patients who are centrally confirmed to be HMR+ will be eligible to enter the screening phase. Patients should be consented to the main study informed consent as soon as HMR positivity is confirmed (recommended within 28 days). Patients will be randomized in a 1:1 ratio to ruxolitinib or placebo on Day 1 following confirmation of eligibility, including confirmed bone marrow fibrosis grading during the 40 day screening period.

### Treatment Period 1

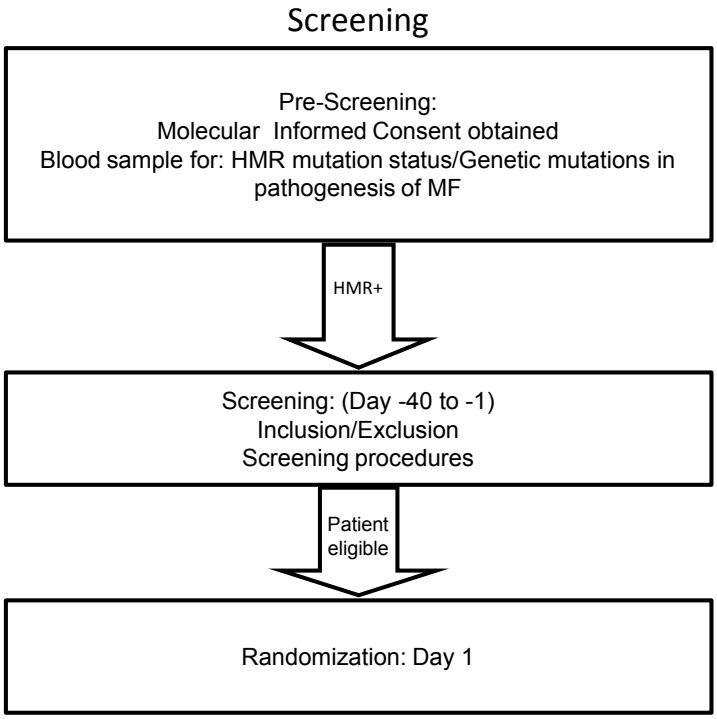
Blinded study treatment will begin on Day 1 following randomization. Visits will be every 4 weeks up to Week 24 to monitor tolerability and efficacy with the study treatment. After Week 24, visits will be every 8 weeks until Week 48, and then every 12 weeks thereafter. Blinded study treatment will be administered until disease progression or patient discontinuation. A 30-day safety follow up visit will be done after the last dose of blinded study drug (except if entering Treatment Period 2). Patients who discontinue for reasons other than disease progression will enter the post treatment follow up. Patients will be followed for survival after end of Treatment Period 1 or post-treatment follow up every 3 months until the termination of study by the sponsor.

## Treatment Period 2

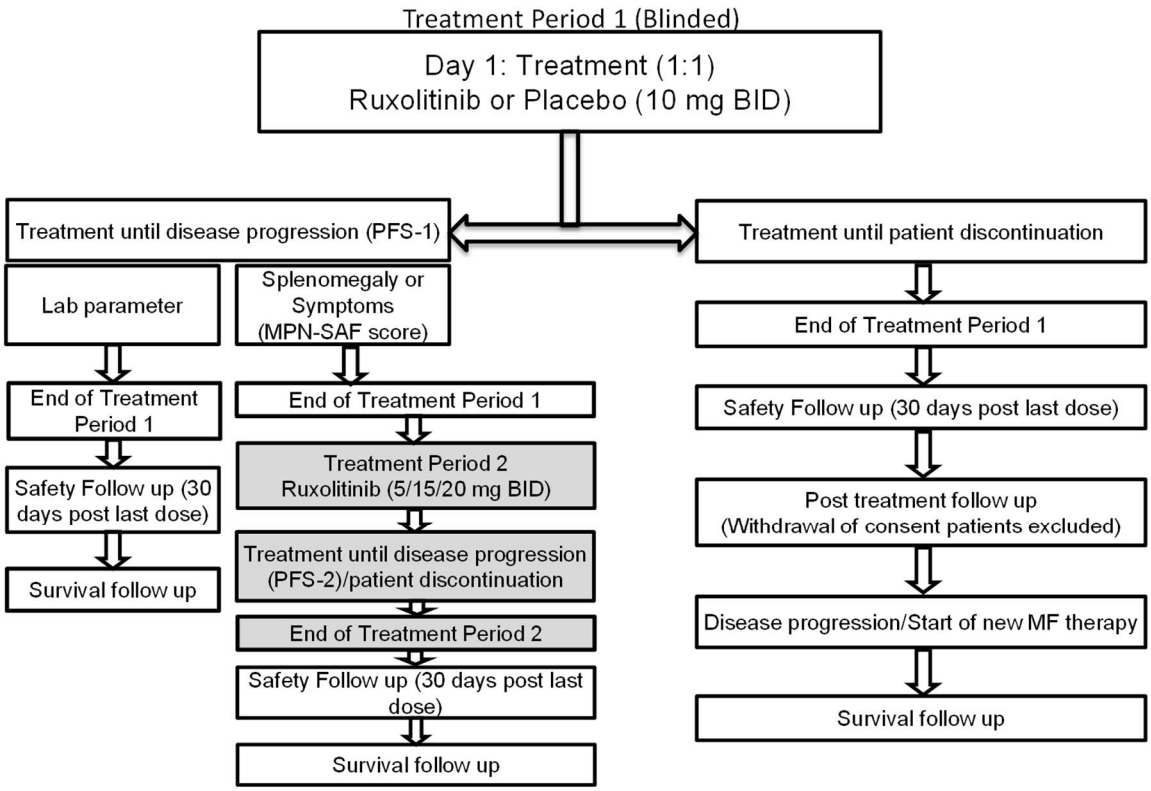
Patients who progress due to splenomegaly or symptoms and are candidates for treatment with currently approved doses of ruxolitinib (as per investigators decision) will be treated with ruxolitinib at 5mg, 15mg or 20 mg BID, based on platelet counts at the time of treatment initiation. These patients will continue on the same schedule of assessments as in 'Treatment Period 1'. A 30-day safety follow up visit will be performed after the last dose of study drug. Patients will be followed for survival after end of Treatment Period 2 every 3 months until the termination of study by the sponsor (Figure 1-1).

**Figure 1-1 Schematic study design**

**A) Screening**



**B) Treatment Period**




## Randomization

Patients will be assigned to one of the two treatment arms in a ratio of 1:1 (ruxolitinib or placebo).

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the IRT provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

Prior to dosing, all patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the patient, which will be used to link the patient to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the patient. The randomization number will not be communicated to the caller.

Randomization is not stratified.

### Interim analysis

The study is terminated prior to initial planned interim analysis due to unresolvable recruitment issue. Hence, one final analysis is planned for the abbreviated CSR and no interim analysis will be performed.

## 1.2 Study objectives and endpoints

Table 3-1 of CINC424A2353 study protocol specifies the study objectives and endpoints. The initial plan of efficacy evaluation and safety assessment of ruxolitinib cannot be implemented due to early termination of the study. The number of patients randomized and the study duration by termination were minimal and they did not provide sufficient information to perform formal comparison specified in the original analysis plan.

To present the efficacy, safety and [redacted] data of interest is the ultimate goal of the early termination study. The key endpoints of interest are listed in Table 1-1below.

**Table 1-1 Endpoints of Interest**

| Endpoint |
|---|
| Change in spleen volume (by MRI/CT) from baseline |
| Change in spleen size (by palpation) from baseline |
| Changes in symptoms using MF-7 and EQ-5D from baseline |
| The frequency, duration, and severity of adverse events including abnormalities in vital signs, laboratory parameters and ECG data |
| [redacted] |
| Plasma ruxolitinib concentrations |
| [redacted] |

# 2 Statistical methods

This section contains information that will be used to draft CSR Section 9.7 on statistical analysis.

## 2.1 Data analysis general information

Data analysis for the clinical study report will be performed by Novartis personnel, Biostatistics and Statistical Programming department.. SAS version 9.4 or later will be used to produce statistical outputs. One final analysis will be performed for efficacy assessments and safety endpoints using data collected up to the cut-off date. The cut-off date is determined by the study termination date.

Only data with an assessment or event start date (e.g., vital sign assessment date or start date of an AE) prior to or on the cut-off date will be included in the analysis. For example: if cut-off date is 15-Jun-2014 then an AE starting on 13-Jun-2014 will be reported, whereas an AE with start date on 17-Jun-2014 will not be reported.

All events with start date before or on the cut-off date and end date after the cut-off date will be flagged as ‘continuing at the cut-off date’. The same rule will be applied to events starting

before or on the cut-off date and not having documented end date. This approach applies, in particular, to adverse event and concomitant medication reports. For these events, the end date will not be imputed and therefore will not appear in the listings. However, for any analysis of duration of AE, the cut-off date will be used for censoring of this event which was ongoing at time of cut-off.

Data post cut-off will not be included in the analysis datasets and not listed.

All participating study centers will be combined for the analysis unless otherwise specified. In general, no center effect will be assessed due to expected small patient enrollment size of centers.

Since the randomization in this study is not stratified, no stratification factors are present.

***Categorical data*** or qualitative characteristics of a subject (e.g., gender, race, subject disposition, etc.) will be summarized by frequency count (number of subjects) and percentages. Percentages will be calculated using the number of subjects in the relevant population or subgroup as the denominator.

***Continuous data*** (e.g., age, body weight, etc.) will be summarized by appropriate descriptive statistics (mean, standard deviation, median, minimum, and maximum).

### 2.1.1 General definitions

**Investigational drug refers to ruxolitinib and study treatment** refers to ruxolitinib or placebo.

### 2.1.2 Date of first administration of study treatment in treatment period 1

The date of first administration of study treatment is defined as the first date when a nonzero dose of study treatment was administered and recorded on DAR TRT1 eCRF. The date of first administration of study treatment in period 1 will also be referred as the ***start date of study treatment***.

### 2.1.3 Date of last administration of study treatment in treatment period 1

The date of last administration of study treatment is defined as the last date when a nonzero dose of study drug was administered and recorded on DAR TRT1 eCRF.

### 2.1.4 Date of first administration of open label ruxolitinib in treatment period 2

The date of first administration of open label ruxolitinib in treatment period 2 is defined as the first date when a nonzero dose of open label ruxolitinib was administered and recorded on DAR TRT2 (ruxolitinib) eCRF.

### 2.1.5 Date of last administration of open label ruxolitinib in treatment period 2

The date of last administration of open label ruxolitinib in treatment period 2 is defined as the last date when a nonzero dose of study drug was administered and recorded on DAR TRT2 eCRF.

### 2.1.6 Last date of study treatment

The last date of study treatment is defined as (1) the date of last administration of study treatment in treatment period 1 if the patient never went to treatment period 2 or (2) the date of last administration of study treatment in treatment period 2 if the patient went to treatment period 2.

### 2.1.7 Study day

The term assessment will be used to represent an evaluation, a measurement or an event (e.g. AE onset, laboratory abnormality occurrence, disease progression, etc)

The study day ***for efficacy assessments*** will be calculated as follows:

Study day = date of assessment – randomization date + 1
*if date of assessment is after the randomization date.*

Study day = date of assessment – randomization date
*if date of assessment is before the randomization date.*

The study day ***for safety assessments*** will be calculated as follows:

Study day = date of assessment – start date of study treatment + 1
*if date of assessment is after the randomization date.*

Study day = date of assessment – start date of study treatment
*if date of assessment is before the randomization date.*

For any assessment or events such as baseline disease characteristics or medical history (e.g., time since diagnosis of disease) that is supposed to occur prior to randomization/start date of the study treatment, study day will be negative. There is no Day 0 defined.

#### Time unit

A year length is defined as 365.25 days. A month length is 30.4375 days (365.25/12). If duration is reported in months, duration in days will be divided by 30.4375. If duration is reported in years, duration in days will be divided by 365.25.

### 2.1.8 Baseline

Baseline values for safety and non-safety evaluations are defined as below unless specified otherwise in the RAP.

For ***safety evaluations*** (e.g. laboratory and vital signs), the last assessment available before or on the start date of study treatment in period 1 (only if such assessment are pre-dose) is taken as a “baseline” assessment.

For ***efficacy and other non-safety evaluations*** (e.g. MRI / CT scan), the last available assessment before or on the day of randomization is taken as the "baseline" value or "baseline" assessment. Multiple assessments on the same day are not expected.

If patients have no assessments as defined above, the baseline result will be missing.

### 2.1.9 Last contact date

The last contact date will be derived for patients not known to have died at the analysis cut-off using the latest complete date among the following:

- Date of randomization
- Last contact date/last date patient was known to be alive from the Survival Follow-up page (if patients status is alive)
- Assessment dates (i.e. vital signs assessment, performance status assessment, and assessment date for spleen imaging, central laboratory, completed PROs)
- Start/end dates from drug administration records and for further antineoplastic therapies
- Adverse events dates including the start and stop date of AEs
- Date of discontinuation from 'End of Treatment' eCRF

The last contact date is defined as the latest complete date from the above list on or before the cut-off date. The cut-off date will not be used for last contact date, unless the patient was seen or contacted on that date. No date post cut-off date will be used.

### 2.1.10 Windows for multiple assessments

In order to summarize data collected over time (including unscheduled visits), the assessments will be time slotted. The following general rule will be applied in creating the assessment windows: If more than one assessment is done within the same time window, the assessment performed closest to the target date will be used. If 2 assessments within a time window are equidistant from the target date, then the later of the 2 assessments will be used. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be listed.

**Table 2-1 Time windows for imaging assessments**

| Time Window | Planned Visit Timing | Time Window Definition |
|---|---|---|
| Screening | Study Days -7 to -1* | Study Days -7-1 |
| Week 12 | Study Day 84 | Study Days 81-87 |
| Week 24 | Study Day 168 | Study Days 161-175 |
| Week 36 | Study Day 252 | Study Days 245-259 |
| Week 48 | Study Day 336 | Study Days 329-343 |
| Every 12 weeks thereafter | | |
| Week y=48+12*k<br>(with k = 1, 2, …) | Study Day (48+12*k)*7 | Study Day<br>Study Day (48+12*k)*7 – 7 to<br>Study Day (48+12*k)*7 + 7<br>Note: EOT data visit are included if obtained within 30 days of last non-zero dose |

| | |
|---|---|
| | intake. |

*Study Day 1 = randomization date
The visits and time windows apply to treatment period 1, 2 and post-treatment follow up, i.e. week 48 visit will be in the same window of 329-343 days in all these periods.

**Table 2-2 Time windows for laboratory and spleen palpation assessments**

| Time Window | Planned Visit Timing | Time Window Definition |
|---|---|---|
| Baseline (Day 1) | On Study Day 1* | Study Days -40-1 |
| Week 4 | Study Day 28 | Study Days 25-31 |
| Week 8 | Study Day 56 | Study Days 49-63 |
| Week 12 | Study Day 84 | Study Days 81-87 |
| Week 16 | Study Day 112 | Study Days 105-119 |
| Week 20 | Study Day 140 | Study Days 133-147 |
| Week 24 | Study Day 168 | Study Days 161-175 |
| Week 32 | Study Day 224 | Study Days 217-231 |
| Week 36 | Study Day 252 | Study Days 245-259 |
| Week 48 | Study Day 336 | Study Days 329-343 |
| Every 12 weeks thereafter | | |
| Week y=48+12*k<br>(with k = 1, 2, …) | Study Day (48+12*k)*7 | Study Day<br>Study Day (48+12*k)*7 – 7 to Study Day (48+12*k)*7 + 7<br>Note: EOT data visit are included if obtained within 30 days of last non-zero dose intake. |

## 2.2 Analysis sets

### 2.2.1 Full Analysis Set

The Full Analysis Set (FAS) comprises all patients to whom study treatment has been assigned by randomization. According to the intent to treat principle, patients will be analyzed according to the treatment they have been assigned to during the randomization procedure.

### 2.2.2 Safety Set

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

Patients will be analyzed according to the study treatment received, where treatment received is defined as the randomized treatment if the patient took at least one dose of that treatment or the first treatment received in the randomized treatment was never received.

### 2.2.3 Per-Protocol Set

Not Applicable for this prematurely terminated study.

### 2.2.4 Pharmacokinetic analysis set

Not Applicable for this prematurely terminated study.

### 2.2.5 Subgroup of interest

Not Applicable for this prematurely terminated study.

### 2.2.6 Withdrawal of Informed Consent

Any data collected in the clinical database after a subject withdraws informed consent from all further participation in the trial, will not be included in the analysis data sets. The date on which a patient withdraws full consent will be recorded in the eCRF.

Death events in some countries can be reported if the death event can be confirmed to be captured from public records (registers). If confirmed, the events will be included in the analysis.

Third party data e.g. PK, [redacted] etc., collected in the clinical database without having obtained consent for collection will not be included in the analysis data sets. These data will be excluded by the presence of the appropriate protocol deviation criterion.

## 2.3 Patient disposition, demographics and other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively by treatment group for the FAS.

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

Demographic characteristics to be summarized: age, sex, race, ethnicity, weight, height, BMI, and ECOG performance status.
Disease characteristics: type of MF, baseline spleen size and volume, MF-7 score, prior MF treatment, JAK2 mutation status, CALR mutation status, MPL mutation status, HMR mutation status, number of individual mutations, baseline hemoglobin level (as continuous variable and relative to 10g/dL), platelet count (as continuous variable and relative to 75,000/μL), absolute neutrophil count (ANC) (continuous variable and relative to 1000/μL), white blood count (continuous variable and relative to WBC > 15 x $10^3$/ μL).

### 2.3.1 Patient disposition

The number of patients who had molecular pre-screening, number of screened patients and number of patients randomized will be tabulated. This summary will be produced for all pre-screened patients. Reasons for screening failure will be summarized and listed.

Patient disposition will be tabulated for the treatment period 1. FAS will be used for these summaries. The summary will include the number of patients who were randomized, treated, ongoing, permanently discontinued from treatment period 1 and went to treatment period 2. Patient disposition for both treatment period 1 and treatment period 2 will be listed.

The following summaries will be provided: % based on the total number of FAS patients:

- Number (%) of patients who were randomized (based on data from IRT system)
- Number (%) of patients who were randomized but not treated (based on 'DAR' eCRF page not completed for any study treatment component)
- Primary reason for not being treated (based on "End of Treatment Phase Completion" eCRF page)
- Number (%) of patients who were treated (based on 'DAR' eCRF pages of each study treatment component completed with non-zero dose administered)
- Number (%) of patients who are still on-treatment (based on the 'End of Treatment Phase' page not completed);
- Number (%) of patients who discontinued the study treatment phase (based on the 'End of Treatment Phase' page)
- Primary reason for study treatment phase discontinuation (based on the 'End of Treatment Phase' page)
- Number (%) of patients who have entered the post-treatment follow-up (based on the 'End of Treatment Phase' page);
- Number (%) of patients who have discontinued from the post-treatment follow-up (based on the Study Evaluation Completion/ End of Post-treatment follow-up page);
- Reasons for discontinuation from the post-treatment follow-up (based on Study Evaluation Completion/ End of Post-treatment follow-up page);
- Number (%) of patients who have entered the survival follow-up (based on the 'End of Treatment Phase' or 'End of Post-treatment follow-up' page).

### Protocol deviations

The number (%) of patients in the FAS with any protocol deviation will be tabulated by deviation category (as specified in the study Data Handling Plan) overall and by treatment group for the FAS. Major protocol deviations leading to exclusion from analysis sets will be tabulated separately overall and by treatment group. All protocol deviations will be listed.

### Analysis sets

The number (%) of patients in each analysis set will be summarized by treatment group.

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

The safety set will be used for the analyses below.

The average daily dose, cumulative dose, duration of exposure in treatment period 1 to ruxolitinib or placebo, dose intensity will be listed and summarized by treatment group. Duration of exposure and duration of follow up will be categorized into time intervals; frequency counts and percentages will be presented for the number (%) of subjects in each interval. The number (%) of subjects who have dose reductions or interruptions, and the reasons, will be summarized by treatment group.

The dose administration records for both treatment period 1 and treatment period 2 will be listed, including the duration of exposure for patients who will enter treatment period 2.

Concomitant medications including prohibited medications, and significant non-drug therapies prior to and after the start of the study treatment will be summarized for all patients and by treatment group.

### 2.4.1 Study treatment / compliance

**Duration of exposure in treatment period 1** is considered by taking into account the duration of exposure to ruxolitinib or placebo.

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

**Duration of exposure in treatment period 2** is considered by taking into account the duration of exposure to open label ruxolitinib.

Duration of exposure in treatment period 2 (days) = (date of last administration of study treatment in treatment period 2) – (date of first administration of study treatment in treatment period 2) + 1.

Summary of duration of exposure in treatment period 1 of study treatment in appropriate time units will include categorical summaries and continuous summaries (i.e. mean, standard deviation etc) using appropriate units of time.

**Duration of follow up** is defined as last contact date – randomization date + 1.

The **average daily dose** refers to the actual daily dose administered.

The **cumulative dose in treatment period 1** refers to the total actual dose administered, over the duration exposure in treatment period 1.

**Dose intensity in treatment period 1** (DI1) for subjects with non-zero duration of exposure in treatment period 1 is defined as follows:

DI1 (mg/day) = Actual Cumulative dose in treatment period 1 (mg) / Duration of exposure to study treatment in treatment period 1 (days).

The number of subjects who have dose reductions, permanent discontinuations or interruptions, and the reasons, will be summarized separately for each of the study treatment components.

‘Dose changed’, ‘Dose interrupted’, and ‘Dose permanently discontinued’ fields from the Dosage Administration CRF pages (DAR) will be used to determine the dose reductions, dose interruptions, and permanent discontinuations, respectively.

The corresponding fields ‘Reason for dose change/dose interrupted’ and ‘Reason for permanent discontinuation’ will be used to summarize the reasons.

For the purpose of summarizing interruptions and reasons, in case multiple entries for interruption that are entered on consecutive days with different reasons will be counted as

separate interruptions. However, if the reason is the same in this block of entries, then it will be counted as one interruption.

The protocol allows use of dose tapering strategy for patients who permanently discontinue study treatment and a separate summary will be produced with the number of patients for whom dose tapering will be recorded in treatment period 1 and treatment period 2.

### 2.4.2 Prior, concomitant and post therapies

#### Prior MF therapy

Prior medications to treat MF will be listed and summarized by ATC class, preferred term, overall and by treatment group by means of frequency counts and percentages using FAS.

#### Post treatment anti-cancer therapy

Anti-neoplastic therapies since discontinuation of study treatment will be listed and summarized by ATC class, preferred term, overall and by treatment group by means of frequency counts and percentages using FAS.

#### Concomitant medications

Concomitant therapy is defined as all interventions (therapeutic treatments and procedures) other than the study treatment administered to a patient coinciding with the study treatment period. Concomitant therapy include medications (other than study drugs) starting on or after the start date of study treatment or medications starting prior to the start date of study treatment and continuing after the start date of study treatment.

Concomitant medications will be coded using the <World Health Organization (WHO) Drug Reference Listing (DRL) dictionary that employs the WHO Anatomical Therapeutic Chemical (ATC) classification system and summarized by lowest ATC class and preferred term using frequency counts and percentages. Surgical and medical procedures will be coded using MedDRA and summarized by SOC and preferred term. These summaries will include:

1. Medications starting on or after the start of study treatment but no later than 30 days after start of last dose of study treatment and
2. Medications starting prior to start of study treatment and continuing after the start of study treatment.

All concomitant therapies will be listed. Any concomitant therapies starting and ending prior to the start of study treatment or starting more than 30 days after the last date of study treatment will be flagged in the listing. The safety set will be used for all concomitant medication tables and listings.

## 2.5 Analysis of the primary objective

The study was terminated prematurely with insufficient sample size and study duration to evaluate the effect of ruxolitinib in delaying progression of MF from early disease to more advanced disease stages. Therefore, the initial primary end point, progression free survival

(PFS), will not be derived and no statistical hypothesis will be tested. Consequently, no supportive analysis for per protocol set is planned.

The early terminated study aims to present data collected for the endpoints of interest, including change in spleen volume and length from baseline, change in symptoms using MF-7 and EQ-5D from baseline (see patient reported outcomes section), safety endpoints [redacted] Descriptive statistics will be used to summarize the endpoints of interest and the FAS will be used for analyzing the data. Change in spleen volume and palpable spleen length below costal margin

Regular assessments of spleen volumes via Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) are performed to evaluate progressive splenomegaly. Spleen size is assessed by palpation and measured in centimeters using a soft ruler, from the coastal margin to the point of greatest splenic protrusion.

Spleen volume, spleen length, absolute change and percentage change in spleen volume by MRI/CT and palpable spleen length below costal margin will be summarized descriptively by treatment for each assessment timepoints.

## 2.6 Analysis of the key secondary objective

There are no key secondary objectives in this study.

## 2.7 Analysis of secondary efficacy objective(s)

No sufficient data were collected to assess the effect of ruxolitinib versus placebo on overall survival and time to progression, so that no secondary efficacy analysis will be performed in this study.

## 2.8 Safety analyses

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

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

**pre-treatment period**: from day of patient's informed consent (molecular pre-screen or main study informed consent) to the day before the first administration of study treatment

**on-treatment period 1**: from day of start of study treatment to minimum of (1) 30 days following the last date of study treatment in period 1 and (2) start of open label ruxolitinib in treatment period 2:

[Start date of study treatment; min(last date of study treatment in treatment period 1 + 30 days, start date of open label ruxolitinib in treatment period 2 – 1 day)].

**on-treatment period 2**: from start day of open label ruxolitinib to 30 days following the last date of study treatment in period 2:

[Start date of open label ruxolitinib in treatment period 2; last date of open label ruxolitinib in treatment period 2 + 30 days].

**post-treatment period**: starting at day 31 after last dose of study treatment.

On-treatment assessment is defined as any assessment reported in the on-treatment period 1 or 2.

Safety summaries (tables, figures) include data from the pre-treatment period (to display the baseline status) and the on-treatment period 1. Data from the on-treatment period 2 (if provided) and the post-treatment period (if provided) with the exception of deaths should not be included.

In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period 1, the so-called ***treatment-emergent*** AEs for period 1.

However, all safety data (including those from the post-treatment period if provided) will be listed and those collected during the pre-treatment, treatment period 2 and post-treatment period will be flagged.

### 2.8.1 Adverse events (AEs)

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 Common Terminology Criteria for Adverse Events] grades, using CTCAE version 4.03), type of adverse event, relation to study treatment by treatment group.

Serious adverse events and non-serious adverse events during the on-treatment period will be tabulated.

All deaths (on-treatment and post-treatment) will be tabulated.

AEs will be summarized by number and percentage of subjects having at least one AE, having at least one AE in each primary system organ class (SOC) and for each preferred term (PT) using MedDRA coding. A subject with multiple occurrences of an AE will be counted only once in the respective AE category. A subject with multiple CTCAE grades for the same preferred term will be summarized under the maximum CTCAE grade recorded for the event.

In AE summaries the primary system organ class will be presented alphabetically and the preferred terms will be sorted within primary SOC in descending frequency. The sort order for the preferred term will be based on their frequency in the ruxolitinib arm.

The following adverse event summaries will be produced by treatment; overview of adverse events and deaths (number and % of subjects who died, with any AE, any SAE, any dose reductions/interruptions), AEs by SOC and PT, summarized by relationship (all AEs and AEs related to study treatment), seriousness (SAEs and non-SAEs), leading to treatment discontinuation, leading to dose interruption/adjustment, requiring additional therapy and leading to fatal outcome. In addition, for the summary of serious and non-serious adverse events the number of occurrences will be produced (an occurrence is defined as >1 day between start and prior end date of record of same preferred term

#### 2.8.1.1 Adverse events of special interest / grouping of AEs

Not planned for this premature termination study.

#### 2.8.1.2 Adverse events of clinical trial safety disclosure

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on adverse events which are not serious adverse events with an incidence greater than 5% and on serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is $\leq 1$ 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 SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a $\leq 1$ day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

### 2.8.2 Deaths

Separate summaries for on-treatment and all deaths (on-treatment and post-treatment) will be produced by treatment arm, system organ class and preferred term. All deaths will be listed, post treatment deaths will be flagged.

### 2.8.3 Laboratory data

Laboratory, data summaries will include all assessments available for the lab parameter collected no later than 30 days after the last study treatment administration date, using data from all sources (central and local laboratories). All laboratory assessments will be listed and those collected later than 30 days after the last study treatment date will be flagged in the listings.

Grade categorization of lab values will be assigned programmatically as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The calculation of CTCAE grades will be based on the observed laboratory values only, clinical assessments will not be taken into account. The criteria to assign CTCAE grades are given in <Novartis internal criteria for CTCAE grading of laboratory parameters>. The latest available version of the document based on the underlying CTCAE version 4.03 at the time of analysis will be used. The Novartis internal CTCAE grading document will be added as appendix to the CSR.

For laboratory tests where grades are not defined by CTCAE v4.03, results will be graded by the low/normal/high (or other project-specific ranges, if more suitable) classifications based on laboratory normal ranges.

A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values,

summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

In rare cases where multiple lab measurements meet the baseline definition, with no further flag or label that can identify the chronological order then the following rule should be applied: If values are from central and local laboratories, the value from central assessment should be considered as baseline. If multiple values are from the same laboratory (local or central) then the value with the last sequence/repeat number should be considered as baseline.

A listing of laboratory values will be provided by laboratory test, patient, and study day. A separate listing will display notable laboratory abnormalities (i.e., newly occurring CTCAE grade 3 or 4 laboratory abnormalities).

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

- 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)
- listing of all laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.
- Boxplots of hematological parameters (hemoglobin and platelet count) over time

### 2.8.4 Other safety data

Analyses will be performed on the safety set.

#### 2.8.4.1 ECG and cardiac imaging data

A standard 12 lead ECG will be performed at screening, every 48 weeks and at the end of

Treatment, read and interpreted locally per protocol specifications. The ECG data will be listed.

#### 2.8.4.2 Vital signs

Vital sign assessments are performed in order to characterize basic body function. The following parameters were collected: height (cm), weight (kg), body temperature (°C), heart rate (beats per minute), systolic and diastolic blood pressure (mmHg), and respiratory rate (per minute).

#### Data handling

Vital signs collected during on-treatment will be summarized. Values measured outside of on-treatment period will be flagged in the listings.

#### Data analysis

For analysis of vital signs the notable criteria are provided in Table 7-1 below.

**Table 2-3 Notable Criteria for vital signs**

| Vital sign (unit) | Notable high value | Notable low value |
|---|---|---|
| Weight (kg) | increase >= 10% from baseline | decrease >= 10% from baseline |
| Systolic blood pressure (mmHg) | >=180 and increase from baseline of >=20 | <=90 and decrease from baseline of >=20 |
| Diastolic blood pressure (mmHg) | >=105 and increase from baseline of >=15 | <=50 and decrease from baseline of >=15 |
| Pulse rate (bpm) | >=100 and increase from baseline of >25% | <=50 and decrease from baseline of >25% |
| Body temperature (°C) | >= 39.1 | -- |

Summary table will be produced for vital signs. The table will include descriptive statistics at baseline, one or several post-baseline time points and change from baseline to this/these post-baseline time points.

A listing of all vital sign assessments will be produced by treatment arm and notable values will be flagged. In the listing, the assessments collected outside of on-treatment period will be flagged as well as assessments made in treatment period 2.

## 2.9 Pharmacokinetic endpoints

All individual plasma ruxolitinib concentration data will be listed for the Full analysis set.

**Handling of PK data below LLOQ or missing**

All concentration values below the lower limit of quantitation (LLOQ) (0.50 ng/mL) are set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. Missing values for any PK data will not be imputed and will be treated as missing.

[redacted]

## 2.11 Patient-reported outcomes

There are several patient reported outcomes measured in the study, including the Myeloproliferative Neoplasm-Symptom Assessment Form (MF-7) Total Symptom Score, the EQ-5D and [redacted]. The FAS will be used for analyzing PRO data. No formal statistical test will be performed.

### Change in symptoms using MF-7

The MF-7 total symptom score is among the key patient reported outcome variables of interest. It will be used to collect data on the impact of ruxolitinib treatment on the patient's disease-related symptoms, functioning and overall quality of life. No formal statistical test

will be performed. Percent change from Baseline in MF-7 total symptom score and 7 individual symptoms at each visit will be summarized with descriptive statistics.

Missing items data in a PRO scale will be handled based on each instrument manual. All PRO analyses will include data as imputed according to the scoring manual. No imputation will be applied if the total or subscale scores are missing at a visit.

### Change in EQ-5D from baseline

The EQ-5D is among the key PRO variables of interest. EQ-5D profiles for each of the five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) will be tabulated by each level (no problems, slight problems, moderate problems, severe problems, and extreme problems) at baseline and each scheduled assessment.

EQ visual analogue scale (VAS) values will be summarized descriptively by arm for each scheduled visit.

The EQ VAS self-rating records of the respondent's own assessment on their health status. The EQ VAS scores are anchored on 100=the best health you can imagine and 0=worst health you can imagine.

Imputation: There should be only ONE response for each dimension. Missing values will be coded as '9'. Ambiguous values (e.g. 2 boxes are ticked for a single dimension) will be treated as missing values.

## 2.13 Bone marrow biopsy and aspirate

The bone marrow biopsy and aspirate assessments data collected at baseline and end of treatment (if available) will be presented in listing. The bone marrow fibrosis is graded according to the IWG consensus criteria for treatment response (Tefferi 2013) and bone marrow blast count in percentage is measured for leukemic transformation.

[redacted]

## 2.15 Interim analysis

Not applicable.

# 3 Sample size calculation

Not applicable.

# 4 Change to protocol specified analyses

Not applicable.

# 5 Appendix

## 5.1 Imputation rules

### 5.1.1 Study drug

Any partial dates or gaps between dates should be resolved. The end date of study drug is derived by using the last non-zero dose end date from the dose administration record CRF page.

If after DBL the partial dates still exist for end date, the imputation rule is as below:

If Month and Year is present, but day is missing, set the end date to be the first day of the month. If after imputation of day, study medication end date is earlier then study medication start date set study medication end date to study medication start date.

### 5.1.2 AE date imputation

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.

### 5.1.3 Concomitant medication date imputation

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.

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 5-1.

**Table 5-1 Allocation of concomitant medications**

| If | Prior Medication | Treatment Phase |
|---|---|---|

| 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 |

#### 5.1.3.1 Prior therapies date imputation

Partial end date of prior therapies date imputation rules are as below:
If only day missing then impute to be 15th of month but should be seven days prior to the start date of study drug. If month and day missing then impute last month and day of year but should be seven days prior to the start date of study drug. If entire date is missing then leave as missing.

#### 5.1.3.2 Post therapies date imputation

**Start date:**

- If Day is missing, then impute to the max (reference start date, first day of the month).
- Day and month are missing then impute to the max(reference start date, Jan 1)
- Reference start date will be last date of study treatment administration + 1.

**End date:** No imputation

#### 5.1.3.3 Other imputations

#### Missing death date

For cases when either day is missing or both month and day are missing for the date of death, the following imputation rules will be implemented:

- If only day is missing, then impute max [(1 mmm-yyyy), min(last contact date+1 , cutoff date)].

If both day and month are missing, then impute max [(1 Jan-yyyy, min (last contact date +1, cutoff date)].

## 5.2 AEs coding/grading

Adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology. AEs are graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

The CTCAE represents a comprehensive grading system for reporting the acute and late effects of cancer treatments. CTCAE grading is by definition a 5-point scale generally corresponding to mild, moderate, severe, life threatening, and death. This grading system inherently places a value on the importance of an event, although there is not necessarily proportionality among grades (a grade 2 is not necessarily twice as bad as a grade 1). The

CTCAE grade of 5 (death) is not used; rather, 'fatal' is collected as AE outcome and death information is also collected on a separate (e)CRF page.

## 5.3 Laboratory parameters derivations

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

As CTC only grades lab values as grade 1-4, grade 0 will be used when lab value is normal. A severity grade of 0 will be assigned for all non-missing lab values not graded as 1 or higher. Grade 5 will not be used. For laboratory tests that are graded for both low and high values, summaries will be done separately and labelled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

If sites report WBC differential counts in percentage (%) with corresponding lab normal ranges in terms of %, the % differentials will be converted to absolute differentials as:

$$\text{Absolute value} = [\text{Value (\%)}/100] \times \text{WBC}.$$

However, the normal ranges will no longer be applicable after conversion. For such cases, then for CTC grading reporting purposes, the <Novartis internal criteria for CTCAE grading of laboratory parameters>will be referenced to determine the CTC grade.

**Table 5-2 Visit evaluation schedule in respect to the components of the primary endpoint**

## A) Treatment Period 1 (Blinded)

| Visit Name | Category | Molecular Pre-screening | Screening | Treatment Period 1 (Blinded) | | | | | | | | | | | End of treatment (EOT) | Progressive disease (PD) confirmation | Safety Follow up 30 days after last dose | Post treatment follow up | Survival Follow up (Every 3 months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Day 1 | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 32 | Week 36 (MRI / CT) | Week 40 | Week 48+ (every 12 weeks until EOT) | | | | | |
| **Day** | | | **-40 to -1** | **1** | **28** | **56** | **84** | **112** | **140** | **168** | **224** | **252** | **280** | **336+** | | | | | |
| **Visit window (Study day)** | | | | | **+/-3** | **+/-3** | **+/-3** | **+/-3** | **+/-3** | **+/-7** | **+/-7** | **+/-7** | **+/-7** | **+/-7** | | | | | |
| Hematology | D | | x | x | x | x | x | x | x | x | x | | x | x | x | x | | x | |
| MRI/CT | D | | x (-7 to -1) | | | | x | | | x | | x | | x | x | | | x | |
| Bone Marrow biopsy and aspirate | D | | x | x (every 2 years) | | | | | | | | | | | x | | | x | |
| MF-7 | D | | x | x | x | x | x | x | x | x | x | | x | x | x | x | x | x | |

## B) Treatment Period 2 (Ruxolitinib) for patients progressing due to splenomegaly or symptoms (MF-7 score)

| Visit Name | Category | Treatment Period 2 (Ruxolitinib) | | | | | | | | | | | End of treatment (EOT) | Progressive disease (PD) confirmation | Safety Follow up 30 days after last dose | Survival Follow up (Every 3 months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | First dose – Ruxolitinib | Week 4 | Week 8 | Week 12 | Week 16 | Week 20 | Week 24 | Week 32 | Week 36 (MRI / CT) | Week 40 | Week 48+ (every 12 weeks until EOT) | | | | |
| Day | | | 28 | 56 | 84 | 112 | 140 | 168 | 224 | 252 | 280 | 336+ | | | | |
| **Visit window (Study day)** | | | **+/-3** | **+/-3** | **+/-3** | **+/-3** | **+/-3** | **+/-7** | **+/-7** | **+/-7** | **+/-7** | **+/-7** | | | | |
| MRI/CT | D | | | | x | | | x | | x | | x | x | | | |
| MF-7 | D | | x | x | x | x | x | x | x | | x | x | x | x | x | |

# 6 Reference

Tefferi et al (2013) Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood. 2013;122(8):1395-1398.