Study PAC203

Statistical Analysis Plan

Version: 3.0

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An Open-Label, Randomized, Phase 2 Dose-Finding Study of Pacritinib in Patients with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis Previously Treated with Ruxolitinib

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Modification	Rationale
Restructured the layout of the SAP to include separate sections for variables definitions and analyses	Reorganization of this document aimed to improve the presentation of the statistical analysis information.
Added data convention	Added details on the data conventions that will be used for data reporting.
Disposition	Added details and clarification of data summaries
Updated the Safety Population	The safety population was modified to define the subject's actual treatment as the initial dose taken since per protocol dose could have been modified (reduced).
PK/PD analyses	These analyses were removed from the statistical analysis plan as a separate PK/PD analysis plan is available.
Excluded the Per Protocol Population and modified the Full Analysis Population to evaluate randomized and treated patients and not condition on having available endpoint data at Week 24.	Following a conservative approach in order to be more data inclusive these populations were modified (excluded) in order to include all randomized and treated subjects in the analysis.
Added reporting of the Progressive Disease information and Physical Examination	Data on progressive disease and physical examinations were collected throughout the study however data reporting was not specified in previous SAP versions.
Excluded TSS evaluation of treatment effects (GEE analysis) and the dose response using the moving average.	The primary aim of this study is to establish the optimal dose with no plan for a formal statistical hypothesis testing. GEE analysis is not considered integral to evaluate the study efficacy objectives
Excluded '30 day Post-EOT' visit from the evaluation of 'worst' value at post-baseline	Safety measures are focused on assessments performed while on study treatment or within 30 days after treatment ended.
Exclusion of the Interim Analysis	The implementation of the BPP futility rule in PAC203, based on spleen volume reduction (SVR), was flawed as assumptions for SVR were based on response rates observed in the completed Phase 3 studies. This misrepresents the population under study in PAC203. For instance, some patients in the PERSIST-2 population had prior JAK inhibitor exposure, however all patients enrolled in the PAC203 study must have prior JAK inhibitor exposure.

	Following mid-year 2018 meetings with the FDA and EMA, and in consultation with the IDMC, the interim efficacy analysis based on a BPP futility rule of SVR was removed so that the study objective of identifying an optimal dose is informed by efficacy, safety, pharmacokinetic and pharmacodynamic data from a fully enrolled study.
Expanded the analysis windows of the SPV, TSS and PGIC	To minimize missing data while keeping clinical relevance.
Expanded the windows of the labs and vital signs information	A modification to the 'EOT' and '30 day-post EOT' analysis windows was made to align the safety assessments with the visit schedule as specified in the protocol calendar of assessments.
Added ECG categories and plots	Following the E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic safety guidelines
Added information to the prior and concomitant medication definitions section	Added the definitions for prior and concomitant medications and specified reports by myelofibrosis indication
Added ECOG definition and reports	Added information on the EGOC scale and the definition for each category. In addition added the summary reports.
Added PGIC and spleen variables definitions	These efficacy variables were not defined previously in the document however analyses of this information was specified in the protocol.
Subgroups of Efficacy	Clarification of clinically meaningful groups
Added information on imputation of the concomitant medications and transfusions	Added instruction for handling missing dates for prior and concomitant medications as well as for transfusions.

1. SCOPE

This document describes the statistical analyses and data presentations to be performed for protocol PAC203, "An Open-Label, Randomized, Phase 2 Dose-Finding Study of Pacritinib in Patients with Primary Myelofibrosis, Post-Polycythemia Vera Myelofibrosis, or Post-Essential Thrombocythemia Myelofibrosis Previously Treated with Ruxolitinib".

This statistical analysis plan (SAP) provides a detailed description of the strategy, rationale, and statistical techniques to be used to determine the most appropriate dosage of pacritinib for future studies. It provides additional details concerning the statistical analyses that were mentioned in the protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified as post hoc in the clinical study report.

2. STUDY OBJECTIVES AND HYPOTHESES

2.1 STUDY OBJECTIVES

2.1.1 Primary Objective

The primary objective is to determine a recommended dosage of pacritinib for further clinical studies.

2.1.2 Secondary Objectives

The secondary objectives are as follows:

1. To examine the dose-response relationship for efficacy, as measured by spleen volume reduction (SVR) using MRI or CT and total symptom score (TSS) using the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score version 2.0 (MPN-SAF TSS 2.0; protocol Appendix 3)
2. To examine the dose-response relationship for safety with a focus on AEs of interest
3. To further characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of pacritinib
4. To evaluate the long term efficacy and safety of pacritinib treatment

1.1 Hypotheses

As this study is designed to explore the dose-response relationship for pacritinib among primary and secondary myelofibrosis (MF) patients and to determine a recommended dosage for further clinical studies, there is no formal statistical hypothesis to be tested.

3. SUMMARY OF STUDY DESIGN

This is a dose-finding study in patients with myelofibrosis who were previously treated with ruxolitinib, are highly symptomatic (DIPSS risk score of Intermediate-1 to High Risk), and have splenomegaly (assessed by physical examination). The study is designed to support a pacritinib dosage selection decision, the process of which will be based on pre-specified efficacy and safety parameters and assessed by an independent data monitoring committee (IDMC).

Spleen volume will be measured by MRI or CT at baseline and Weeks 12 and 24. Safety will be monitored with physical examinations, clinical laboratory assessments (including hematologic, chemistry, and coagulation testing), and cardiac monitoring (including ECG and echocardiogram testing); specified study treatment dosage modifications will be followed to address identified abnormalities. Adverse event data will be collected throughout the study.

Three dosages will be evaluated; pacritinib 100 mg QD, pacritinib 100 mg BID, and pacritinib 200 mg BID. During the study, the interim data will be reviewed by the IDMC for the determination of dropping treatment arm(s), which will be guided by

- The results of interim analyses evaluating the Bayesian predictive probability (BPP) of clinically meaningful SVR (details in section 7.4),
- Safety reviews, with occurrence of 2 treatment-emergent CTCAE grade ≥4 cardiac AEs or 2 treatment emergent CTCAE grade ≥4 hemorrhage AEs in any arm being of particular concern, and
- Other efficacy and safety measures.

Assigned treatment will continue for 24 weeks unless the patient experiences progressive disease, intolerable AEs, or withdraws consent, or until the assigned treatment arm is closed. Once an arm is closed, patients in that arm will discontinue the study. No study treatment crossover will be allowed. The maximum duration of trial participation for an individual patient will be approximately 3 years.

4. RANDOMIZATION AND BLINDING

Initially, eligible patients will be centrally randomized in a 1:1:1 allocation ratio to pacritinib 100 mg QD, pacritinib 100 mg BID, or pacritinib 200 mg BID using a central interactive web response system (IWRS). If interim analysis indicates that any one of the treatment arm meets the stopping

criteria (protocol Sections 11.8 and 11.9) for efficacy or safety and is thus dropped, then the randomization will be updated to a 1:1 ratio of the two remaining study arms. In the case of two arms being dropped by interim efficacy or safety monitoring, all eligible patients will be enrolled to the remaining one active arm until up to 30 evaluable subjects are enrolled in that arm. The dropping of a treatment arm is effected in the IWRS by disabling randomization to the relevant treatment arm. Thus, the treatment arm being dropped will not be available as an option for treatment assignment at randomization.

The randomization will be stratified by geographic region (North America vs. Europe vs. rest of the world (RoW)) and baseline platelet count (≤50,000/μL vs. >50,000/μL to ≤100,000/μL vs. >100,000/μL). Permuted blocks of size 3 will be used within each stratum to balance the treatment allocation. The treatment codes and descriptions for the treatment arms are:

- 1: PAC 100 mg QD (100 mg of pacritinib once daily)
- 2: PAC 100 mg BID (100 mg of pacritinib twice daily), and
- 3: PAC 200 mg BID (200 mg of pacritinib twice daily).

This study is an open-label study. A patient's treatment assignment will be known to all except the independent radiographic and cardiology assessors who will remain blinded to patient treatment assignment throughout the study.

5. ANALYSIS POPULATIONS AND APPROACHES TO ANALYSIS

5.1 FULL ANALYSIS SET

The full analysis set (FAS) is defined as all randomized patients who received at least one dose of study treatment. Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. The FAS will serve as the population for the analyses of efficacy, in keeping with the intent-to-treat (ITT) principle. Analyses of efficacy will provide an indication of potential benefit in the exploration to determine the recommended dose of pacritinib for further clinical studies.

5.2 SAFETY POPULATION

The safety population is defined as all randomized patients who received at least one dose of study treatment.

All safety analyses will be performed using the safety population, and patients in this population will be analyzed according to the treatment actually received. Treatment actually received will be

determined by the treatment initially taken. Safety analyses will provide an indication of potential risk in the exploration to determine the recommended dose of pacritinib for further clinical studies.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1 DATA ANALYSIS CONVENTIONS

All data analysis will be performed by CTI or designee after the study is completed and the database has been locked and released. Statistical programming and analyses will be performed using SAS® version 9.4. Outputs will be provided in both RTF and PDF for tables, listings and figures using landscape orientation. Applicable study data will be listed at minimum by subject, treatment arm, and visit (as applicable) based on the analysis population as specified in this plan.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), minimum, first quartile (Q1), median, third quartile (Q3), and maximum. Summaries of discrete variables will include frequency counts and percentages.

6.2 MULTIPLICITY

No formal statistical hypothesis testing will be performed, thus no multiplicity adjustment is needed.

7. DISPOSITION AND ENROLLMENT

Patient disposition will be presented as number and percentages of patients who were screened, randomized, completed the study, and discontinued the study. A completed patient will be one who has not been discontinued or withdrew consent from the study. Disposition will be summarized by treatment arm and for all study patients.

The number and percentage of patients prematurely discontinued from the study and the reasons for study discontinuation will be summarized for all randomized patients. The reasons for study termination include: withdrawal by patient, lost to follow-up, death, study termination by sponsor, physician decision and other reasons. In addition, the number of patients who discontinued treatment as well as the reasons for treatment discontinuation (adverse event, death, lost to follow-up, physician decision, study terminated by Sponsor, withdrawal by patient and other reasons) will be presented by treatment arm.

Study enrollment by country and region will be presented by treatment arm.

8. DEMOGRAPHICS, BASELINE CHARACTERISTICS, AND MEDICAL HISTORY

The demographic and baseline characteristics will be analyzed with the following variables in all randomized patients.

8.1 DEMOGRAPHIC VARIABLES

Age, age category (< 65 years vs. ≥ 65 years), gender (female vs. male), race (American Indian or Alaska Native vs. Asian vs. Black or African American vs. Native Hawaiian or Other Pacific Islander vs. White vs. Other vs. Multiple), ethnicity (Hispanic or Latino vs. Non-Hispanic or Latino), height, weight, body mass index, and ECOG performance status (0 vs. 1 vs. 2),.

8.2 BASELINE DISEASE CHARACTERISTIC VARIABLES

Spleen length by physical exam, baseline platelet count and category (≤ 50,000/μL vs. > 50,000/μL to ≤100,000/μL vs. >100,000/μL), baseline hemoglobin and category (< 100 g/L vs. ≥ 100 g/L), peripheral blasts percentage and category (< 1% vs. ≥ 1%), white blood cell count and category (≤ $25x10^9$/L vs. > $25x10^9$/L), current MF diagnosis (PMF vs. PPV MF vs. PET MF), time since current MF diagnosis, gene mutation status (JAK2V617F vs. other JAK2 vs. MPL vs. CALR vs. Triple Negative vs. Other vs. None), abnormal cytogenetics (Yes vs. No), unfavorable karyotype (Yes vs. No), current DIPSS score (1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6), DIPSS plus score (1 vs. 2 vs. 3 vs. 4 vs. 5 vs. 6), transfusion history (within 90 days prior to (Informed Consent date through the treatment start date + 1)), red blood cell (RBC) transfusion dependence as defined by the Gale criteria (Gale et al. 2011; Table 1), and platelet transfusion dependence (Table 2).

Table 1 – Definitions of Red Blood Cell Transfusion Dependence and Independence

	RBC Transfusions
RBC transfusion dependence	≥ 2 units/month
RBC transfusion independence	None
Reduced RBC transfusion dependence	50% decrease
Gale et al. 2011	

Table 2 – Definitions of Platelet Transfusion Dependence and Independence

	Platelet Transfusions
Platelet transfusion dependence	Any episode of platelet transfusion during the past month
Platelet transfusion independence	No platelet transfusion during the past month

8.3 PRIOR THERAPY AND CONCOMITANT MEDICATIONS

Prior therapy is any therapy or medication taken prior to informed consent. Prior therapy includes both prior MF and non-MF therapies. Both will be summarized for all enrolled patients by treatment and overall.

A medication will be considered a concomitant medication if it was taken by the patient at any time on study (on or after the first day of treatment and within 30 days after the last dose of study drug). The following will also be considered concomitant medications:

- Medications missing both start and stop dates.
- Medications having a start date prior to the last dose of study drug and missing the stop date.

Concomitant medications will be summarized by ATC class and preferred term in each treatment arm. Prior MF and non-MF therapies or medications will be summarized by Anatomic Therapeutic Chemical (ATC) class and preferred term using WHO Drug Dictionary version 01, March 2013.

8.4 Prior Ruxolitinib Experience

The experience of patients with prior ruxolitinib therapy will be summarized as well. Descriptive statistics for the following characteristics will be presented by treatment arm and overall: prior ruxolitinib treatment experience, ruxolitinib treatment duration, time since last ruxolitinib treatment, most recent ruxolitinib total daily dose and dose category (< 10 mg/day vs. ≥ 10 mg/day), highest ruxolitinib total daily dose, the lowest hemoglobin at start of and on ruxolitinib therapy, RBC transfusion requirements prior to and at the end of ruxolitinib therapy, the lowest platelet count at start of and on ruxolitinib therapy, and adverse events experienced, patients with reduction in spleen length and volume, and patients with clinically meaningful reduction in symptoms while on ruxolitinib therapy. The reasons for discontinuing ruxolitinib therapy will also be summarized.

8.5 Medical History

Medical history is any disease that occurred prior to informed consent. Medical history will be summarized by frequency distribution (n and %) of system organ class and preferred term by MedDRA dictionary version 16.0 for all enrolled patients.

9. EXPOSURE TO STUDY TREATMENT

Exposure to study treatment will be evaluated by the duration of treatment, cumulative dose, actual dose intensity, and relative dose intensity in the safety population.

Duration of treatment (weeks): is defined as the duration from first day of study treatment to the last day of study treatment, i.e.,

$$\frac{(\textit{Date of last dose of study treatment} - \textit{date of first dose of study treatment} + 1)}{7}.$$

Descriptive statistics will be provided for duration of treatment by treatment arm.

Cumulative dose (mg): is defined as the sum of all doses of study treatment taken and descriptive statistics will be provided by treatment arm. The counts and percentages of patients with any dose modifications will be provided by treatment arm. Reasons for dose modifications will also be summarized.

Actual dose intensity (ADI, mg/day) = (total dose taken in mg) ÷ (duration of treatment in days) and descriptive statistics will be provided by treatment arm.

Relative dose intensity (RDI, %) = (ADI) ÷ (planned daily dose) * 100. The planned pacritinib dose is 100, 200, and 400 mg/day in the pacritinib 100 mg QD, 100 mg BID, and 200 mg BID arms, respectively. Descriptive statistics will be provided by treatment arm.

Study drug modification categories will be defined for drug holds and drug reduction. Drug holds will be identified by those records with dose entered as 0mg. Drug reduced will be identified by evaluating the subject's initial dose and determining if a reduction occurred at any time during the treatment period.

Finally, reasons for drug modifications will be presented by treatment arm.

10. EFFICACY VARIABLES

The primary efficacy variable for dosage selection is the percent reduction in spleen volume from baseline as measured by MRI or CT at Weeks 12 and 24.

Other supportive measures for evaluation as part of the dose-response relationship include

- the percentage of patients who achieve at least 35% reduction in spleen volume
- % TSS reduction from baseline, and
- the percentage of patients with at least 50% reduction in TSS.

The planned analyses for the efficacy endpoints of the study are detailed in the subsections below and will be performed in the full analysis set.

10.1 Spleen volume (SPV)

Spleen volume will be measured by MRI (preferred) at baseline and Weeks 12 and 24 or end of treatment visit if imaging did not occur at the end of Week 24. Unscheduled imaging assessments may be performed at physician discretion if he/she considers disease-related symptoms to be worsening. Patients who cannot undergo MRI, or for whom MRI is not available will assess spleen volume by CT scan. However, for each patient, the same imagining modality will be used throughout the study. An independent radiologist, blinded to all patient and site identifiers as well as treatment assignments, will measure spleen volume. While images generated as part of unscheduled visits may be read locally if treatment discontinuation is being considered, only the scheduled centrally read images will be used for the efficacy analysis.

The percent reduction and the proportion of subjects with a ≥ 35% spleen volume reduction will be computed as follows:

$$\textbf{SPV \% Reduction} = -\left(\frac{\text{Week 12 or 24 SPV - Baseline SPV}}{\text{Baseline SPV}}\right) * 100$$

$$\textbf{Proportion of subject with SPV reduction} \geq \textbf{35\%} = \left(\frac{\text{Number of subjects with} \geq 35\% \text{ SPV reduction}}{\text{Number of subjects in the FAS population}}\right)$$

10.2 Total Symptom Score (TSS)

The MPN-SAF TSS 2.0 is an instrument measuring disease impact among patients with Myelofibrosis (MF). Supportive measures of efficacy are the percent change from baseline in TSS as measured by the MPN-SAF TSS 2.0 and the proportion of patients with TSS reduction ≥50% at Weeks 12 and 24. Patients will begin reporting symptoms via electronic dairy at least 7 days before starting pacritinib treatment and will continue until the Week 48 visit. After Week 48, patients will complete a 7-day recall version of the symptom assessment at each study visit.

TSS Algorithm

- **The daily TSS** is the sum of the scores for the following symptoms: tiredness, early satiety, abdominal discomfort, night sweats, pruritus, bone pain, and pain under ribs on the left side (excludes the inactivity score).

- **The baseline TSS** is the mean of the daily TSS over the 7 consecutive days prior to the start of treatment. Missing values during these days are handled as described below (section 7.2.2).

- **Week 24 TSS** is the mean of the daily TSS obtained during the 28 consecutive days prior to the post-baseline spleen volume scan date (i.e. Week 12 or 24 visit date if scan date is

missing). A similar approach will be performed when defining the TSS values for Weeks 12, 36 and 48.

- The percent reduction in TSS from baseline to the Week 12 or 24 visit is computed by:

$$\text{TSS \% Reduction} = -\left(\frac{\text{Week 12 or 24 TSS - Baseline TSS}}{\text{Baseline TSS}}\right) * 100.$$

Handling of Missing TSS Values

- If any of the seven individual symptoms scores are missing, the TSS for that day will be considered as missing.

- The baseline TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to the start of study treatment.

- The Week 24 TSS is set to missing if fewer than 20 daily TSS are available out of the 28 consecutive days prior to Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). In sensitivity analyses where Week 24 TSS is derived from the mean of 7 consecutive days of daily TSS, the Week 24 TSS is set to missing if fewer than 4 daily TSS are available out of the 7 consecutive days prior to Week 24 spleen volume scan date (or Week 24 visit date if scan date is missing). Missing TSS at other post-baseline time-points is similarly handled. A similar approach will be performed when defining the TSS values for Weeks 12, 36 and 48.

10.3 Patient Global Impression Assessment

The self-reported measure Patient Global Impression of Change (PGIC) is a 7 point scale depicting a patient's rating of overall improvement. Patients rate their change as 'very much improved', 'much improved', 'minimally improved', 'no change', 'minimally worse' or 'very much worse'. PGIC will be collected at the end of Week 12, the end of Week 24 or the end of treatment visit and every 3 months up to 2.5 years.

10.4 Spleen Length Reduction

Spleen size, assessed by physical examination as the distance below the lower costal margin at the midclavicular line, will be evaluated at study visits Week4, Week 12, Week 24 and every 3 months thereafter up to 2.5 years. The percent change from baseline and the proportion of patients with >50% spleen length (SPL) reduction at 12 and 24 weeks will be computed as follows:

$$\textbf{SPL \% Reduction} = -\left(\frac{\text{Week 12 or 24 SPL - Baseline SPL}}{\text{Baseline SPL}}\right) * 100$$

$$\textbf{Proportion of subject with SPL reduction} \geq \textbf{50\%} = \left(\frac{\text{Number of subjects with} \geq 50\% \text{ SPL reduction}}{\text{Number of subjects in the FAS population}}\right)$$

10.5 Transfusions

10.6.1 Frequency of Red Blood Cell (RBC) Transfusions

The frequency of RBC transfusions at baseline is defined as the number of units of RBC transfusions per month prior to and including the date of the start of treatment. Since this data comes from two different sources, the baseline RBC transfusion frequency is computed as the sum of the number of units of RBC transfusions in the 90 days prior to the informed consent date and the number of units of RBC transfusions after the informed consent date through to the start of treatment date, divided by the number of days from informed consent to the start of treatment plus 90 days, multiplied by a conversion factor of 30 days/month. That is,

$$\frac{(\#\ units\ from\ Transfusion\ History + \#\ units\ from\ IC\ to\ start\ of\ treatment)}{(90 + (treatment\ start\ date - IC\ date + 1))\ days} \times 30\ \frac{days}{month}.$$

At post-baseline timepoints, the frequency of RBC transfusions is defined as the number of units of RBC transfusions per month in the three months (approximately 84 – 90 days) preceding the visit date. That is,

$$\frac{(\#units\ in\ the\ days\ preceding\ the\ visit\ date)}{number\ of\ study\ days\ from\ previous\ visit}\ X\ 30\ \frac{days}{month}$$

10.6.2 Frequency of Platelet Transfusions

The frequency of platelet transfusions at baseline is defined as the number of platelet transfusions per month prior to and including the date of the start of treatment. Since this data comes from two different sources, the baseline platelet transfusion frequency is computed as the sum of the number of transfusions in the 90 days prior to the informed consent date and the number of transfusions after the informed consent date through to the start of treatment date, divided by the number of days from informed consent to the start of treatment plus 90 days, multiplied by a conversion factor of 30 days/month. That is,

$$\frac{(\#\ transfusions\ in\ Transfusion\ History + \#\ transfusions\ from\ IC\ to\ start\ of\ treatment)}{(90 + (treatment\ start\ date - IC\ date + 1))\ days} \times 30\ \frac{days}{month}.$$

At post-baseline timepoints, frequency of platelet transfusions is defined as the number of platelet transfusions in the month (30 days) preceding the visit date.

$$\frac{(\#units\ in\ the\ days\ preceding\ the\ visit\ date)}{number\ of\ study\ days\ from\ previous\ visit}\ X\ 30\ \frac{days}{month}$$

10.7 ECOG Performance Status

The ECOG (developed by the Eastern Cooperative Oncology Group) is scale which describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.). It is a scale from 0 to 5 defined as:

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

11 SAFETY VARIABLES

11.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All AEs, including serious adverse events (SAEs) will be collected during the clinical study from the time the patient signs the informed consent through 30 days following the last dose of study treatment. For screened patients who are not randomized, only

SAEs occurring between the time of informed consent and determination of screen failure are to be reported.

A TEAE is defined as an adverse event (AE) occurring after the first dose of study treatment and within 30 days after the last study treatment date. In addition, an AE with a missing start date but with an end date after the first study drug dose date is also considered a TEAE. An AE occurring after the first dose of study drug that also occurred prior to the first dose of study drug is only considered a TEAE if the AE worsened in grade after the first dose of study drug.

Analysis of AEs will be based on Treatment Emergent Adverse Events (TEAEs).

11.2 SAFETY LABORATORY ASSESSMENTS

Hematology and coagulation function laboratory measures will be collected via central lab, but in addition can be analyzed locally for assessment and management of patients in real time.

11.2.1 HEMATOLOGY

Hematology parameters including CBC, differential, platelet count and hemoglobin A1C among others will be evaluated at screening, baseline, the end of week 4, the end of Week 12, the end of Week 24 or the end of treatment visit, every 3 months during the follow-up period, and 30 days after the last dose of study treatment.

11.2.2 COAGULATION FUNCTION

Coagulation testing will include PT, INR, PTT and TT at screening, baseline, the end of week 4, the end of Week 12, the end of Week 24 or the end of treatment visit, every 3 months during the follow up period, and 30 days after the last dose of study treatment.

11.2.3 CHEMISTRY

Screening laboratory assessments should be performed at least 1 week after the end of prior therapy. Serum chemistry parameters (ALT/SGPT and AST/SGOT, alkaline phosphatase, bilirubin [total, direct, and indirect], creatinine, lactate dehydrogenase (LDH), sodium, potassium, chloride, bicarbonate, calcium, phosphate, magnesium, blood urea nitrogen (BUN/area), albumin, amylase, lipase, glucose, cholesterol, uric acid, and high specificity CRP) will be evaluated by a central laboratory at screening, at baseline and whenever is clinically indicated.

The derived visit window definitions for clinical hematology, chemistry, and coagulation function are displayed in Table 5.

Table 5. Analysis Window Definitions for Clinical Hematology and Coagulation Function Results

Visit	Nominal Day	Range
Baseline	1 (first dose date)	[-14, 1]
Week 4	28	[2, 55]
Week 12	84	[56, 111]
Week 24	168	[112, 195]
Week 36	252	[196, 279]
Week 48	336	[280, 363]
⋮	⋮	⋮
Week XX	XX times 7	[(Week XX-1 upper range + 1, (XX times 7) + 27]
EOT	Last dose date	[Last dose date, Last dose date + 15]
30 days post EOT	Last dose date + 30 days	[Last dose date + 16,]

11.2.4 ECG ASSESSMENT

All patients will have a 12-lead ECGs collected in triplicate and centrally read by a blinded independent cardiologist and QTc intervals, calculated and corrected using the Fredericia method (QTcF), at screening, baseline, the end of Week 4, the end of Week 12, the end of Week 24 or the end of treatment visit, and every 3 months while in the follow-up period (pre-dose only for the post 24-week follow-up visit and 30 days after the last dose of study treatment). Additional ECGs may have been collected in the event patient demonstrated QTc prolongation.

The three QTcF interval measures will be averaged for a summary measure of QTcF interval.

11.2.5 CARDIAC EJECTION FRACTION ASSESSMENT

All patients will have ejection fraction (echocardiogram or MUGA scan) at screening, the end of Week 4, the end of Week 12, the end of Week 24 or the end of treatment visit, and every 6 months while in the follow-up period, and 30 days after the last dose of study treatment.

11.2.6 ADDITIONAL SAFETY ASSESSMENTS

11.2.6.1 Vital signs including pulse, systolic and diastolic blood pressure, respiratory rate, temperature, and body weight.

11.2.6.2 Physical examination, including clinical signs and symptoms, and spleen measurement.

12 EFFICACY ENPOINTS AND ANALYSES

12.1 PRIMARY EFFICACY ENDPOINTS

12.1 1 Spleen Volume Reduction

The primary efficacy variable for dosage selection is the percent reduction in spleen volume from baseline as measured by MRI or CT at Weeks 12 and 24..

Descriptive statistics of spleen volume at baseline, Week 12, Week 24, and at End of Treatment will be presented by treatment arm. Spleen volume at End of Treatment is defined as the spleen volume collected at the end of treatment visit or the last spleen volume measured on treatment if not measured at end of treatment. Descriptive statistics of percent reduction in spleen volume at Weeks 12 and 24 and at End of Treatment will be presented by treatment arm. These descriptive statistics include counts, mean, standard deviation, standard error of the mean, median, 25^{th} percentile, 75^{th} percentile, minimum, and maximum. As a supportive measure of efficacy, the counts and proportions of patients with spleen volume reduction (SVR) ≥35% at Weeks 12 and 24 and at End of Treatment will be presented by treatment arm. The exact (Clopper-Pearson) 95% confidence intervals (CIs) for the proportions will also be presented. Additional supportive analyses include imputing missing Week 24 spleen volume with the previous post-baseline (Week 12) spleen volume, if any, and repeating the above analyses. These analyses will be repeated for spleen volume measured after Week 24 in long term follow up.

12.1 2 Total Symptom Score (TSS) Analysis

Descriptive statistics of individual symptoms and TSS at baseline, every 12 weeks, and at End of Treatment will be presented by treatment arm. Descriptive statistics of percent reduction in TSS every 12 weeks and at End of Treatment will be presented by treatment arm. The counts and proportions (including Clopper-Pearson 95% CIs) of patients with TSS reduction ≥50% every 12 weeks and at End of Treatment will be presented by treatment arm. Supportive analyses include imputing missing Week 24 TSS with the previous post-baseline (Week 12) TSS, if any, and repeating the above analyses at Week 24.

As an anchor for patient-reported symptom assessment, the patient global impression assessment (PGIA) will also be summarized and evaluated for correlation with TSS. There is 1 domain in the PGIA instrument with possible scores ranging from 1 (very much improved) to 7 (very much worse).

12.1 3 Patient Global Impression Assessment

The scores for the PGIA will be summarized by treatment arm at each visit at which the patients are scheduled to complete the instrument using descriptive statistics. Additionally, the correlation between PGIA and TSS and the change in PGIA and change in TSS at each visit assessed will be explored.

12.2 EXPLORATORY EFFICACY ANALYSIS

12.2 1 Spleen Length Reduction

Descriptive statistics of spleen length by physical exam at each visit will be presented by treatment arm. Descriptive statistics of percent reduction in spleen length at each post-baseline visit will be presented by treatment arm. The counts and proportions (including Clopper-Pearson 95% CIs) of patients with spleen length reduction ≥50% at Weeks 12 and 24 will be presented by treatment arm.

12.2 2 Transfusions

The change in the frequency of transfusions will be summarized by treatment arm over time using descriptive statistics in patients receiving at least one transfusion at baseline or while on study treatment. This summary is dependent on the number of patients who received at least one transfusion at baseline or while on study treatment.

12.2 3 ECOG Performance Status

The scores for the ECOG performance status will be summarized by treatment arm at each visit using descriptive statistics such as counts and percent. In addition, the shift from baseline to worst ECOG performance status at post-baseline visits will be presented by treatment arm.

12.1 Subgroup Analyses of Efficacy

If there are enough patients per group, subgroup analyses may be evaluated for any potential impact of demographics or baseline disease characteristics on the efficacy endpoints. Subgroups may include, but are not limited to, baseline hemoglobin (< 100 g/L vs. ≥ 100 g/L), and baseline platelet count (≤ 50,000/μL vs. > 50,000/μL).

13 SAFETY ANALYSES

Safety analyses include summaries and graphical presentations of treatment emergent adverse events, clinical labs, ECG, vital signs, performance status, and any abnormal findings observed during the performance of physical examinations by treatment received after randomization through the end of assigned study treatment + 30 days.

The primary safety measure for dosage selection is the percentage of patients with CTCAE grade 3/4 cardiac treatment-emergent AEs, CTCAE grade 3/4, hemorrhage treatment-emergent AEs, CTCAE grade ≥4 thrombocytopenia toxicity, or CTCAE grade ≥4 anemia toxicity. Cardiac and hemorrhage treatment-emergent AEs will be determined using Standardized MedDRA Query (SMQ). See section 9.1 for more details. Thrombocytopenia and anemia will be determined by central laboratory measurement.

All other safety data including TEAEs, death, and clinical laboratory measures will be used as supportive measures for evaluation of pacritinib dose-safety relationship.

13.1 ADVERSE EVENTS

Treatment-emergent AEs (TEAEs) will be summarized by presenting, for each treatment arm, the count and percentage of patients having any TEAE, having a TEAE in each body system, and having an individual event according to version 16.0 of the MedDRA dictionary. CTCAE (version 4.03) grades and relationship to study medication will be summarized as appropriate. For summaries by CTCAE grade or relatedness, only the highest CTCAE grade or degree of relatedness of each SOC and/or preferred term will be summarized. A patient having the same event more than once will be counted only once and by greatest severity or closest relationship.

In addition, serious TEAEs (SAEs), CTCAE grade 3 or 4 TEAEs, TEAEs leading to study medication discontinuation, interruption, or dose reduction, TEAEs with an outcome of death, and related TEAEs will be summarized. A listing of all SAEs will be generated. The preferred term of TEAEs of all grades, as well as for TEAEs of grade 3 or 4 will also be presented for each treatment arm by decreasing frequency in the PAC 200 mg BID arm.

Cardiac, hemorrhage, skin neoplasms, and hypersensitivity TEAEs as defined by Standardised MedDRA Queries (SMQs) will also be summarized by SOC and preferred term. Cardiac TEAEs are all the preferred terms in the SMQs of Cardiac Arrhythmias, Cardiac Failure, Ischaemic Heart Disease, and Embolic and Thrombotic Events. Hemorrhage TEAEs are all preferred terms in the SMQ of Haemorrhages. Skin neoplasm TEAEs are all preferred terms in the SMQ of Skin Neoplasms (malignant and unspecified). Hypersensitivity TEAEs are all preferred terms in the SMQ

of Hypersensitivity. A listing of time to onset and resolution of these TEAEs will also be presented by treatment arm. These will also be presented graphically.

The counts and percentages for the causes of all deaths will be presented by treatment arm. A listing of all deaths, both on and off treatment, will also be generated. On treatment deaths are defined as deaths that occur on treatment and within 30 days of treatment discontinuation.

13.2 CLINICAL LABORATORY MEASUREMENTS

The counts and percentages of the shifts in CTCAE grade from baseline to the worst and last post-baseline grade (not including the 30 post treatment end visit in the evaluation of worst grade at post-baseline) will be presented for each laboratory measure. Descriptive statistics of change and percent change from baseline in laboratory values will be presented by visit. Plots of the shift from baseline to worst post-baseline in selected parameters by treatment arm will be presented. In the case of hemoglobin, a parameter that is hugely affected by transfusions, the percent change over time will be explored in patients who did not have a transfusion in the 90 days prior to informed consent or on study.

Laboratory results (including serum pregnancy) will be provided in a subject list and include at minimum subject id, age, treatment arm, visit, assessment date, laboratory category, laboratory parameter, results and lab units.

13.3 OTHER CLINICAL SAFETY

13.3.1 ELECTROCARDIOGRAM (ECG)

The frequency distribution of abnormal QTcF interval measurements on study (after the first study drug treatment through the last dose of study drug) will also be summarized. That is, the proportion of subjects with the following QTcF intervals will tabulated by timepoint at each visit (including worst and last on treatment values) and treatment arm:

- A measured value > 450 ms
- A measured value > 480 ms
- A measured value > 500 ms
- 0 - <= 10 ms above baseline
- 10 - 20 ms above baseline

- >= 20 ms above baseline
- 30 ms above baseline
- > 60 ms above baseline

Plots of the shift in QTcF from baseline to highest on treatment will also be presented for each treatment group.

Finally, a plot of the mean change of the QTcF over time will be presented by treatment arm.

13.3.2 ECHOCARDIOGRAM OR MULTIPLE-GATED ACQUISITION SCAN

Change in the left ventricular ejection fraction (LVEF) assessed on study (after the first study drug treatment through the last dose of study drug) will be summarized. Descriptive statistics of change from baseline in LVEF will be presented by treatment arm at each visit, the last post-baseline assessment, and the worst post-baseline assessment (not including the 30-day post treatment end visit in the evaluation of worst grade at post-baseline). At these visits and by treatment arm, the count and percentage of patients with LVEF values ≤50% will also be presented overall and in categories of 50% to 40%, 39% to 20%, and < 20%. Similarly, the count and percentage of patients with decreases in LVEF of ≥10% or more will be presented overall and in categories of 10% to 19% and ≥ 20%.

13.3.3 VITAL SIGN MEASUREMENTS

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) of the actual values and the change from baseline in vital sign measurements, including weight, will be presented by visit.

A table summarizing clinically notable blood pressure and weight measurements which are aligned with CTCAE cut-offs, where available, will be displayed. The proportion of subjects whose worst observed values while on study treatment (on or after the first day of treatment) meet the following clinically notable criteria will be tabulated by treatment arm:

- Systolic Blood Pressure
    - < 85 mm Hg
    - ≥ 140 - < 160 mm Hg
    - ≥ 160 mm Hg

- Diastolic Blood Pressure
    - < 50 mm Hg
    - ≥ 90 - < 100 mm Hg
    - ≥ 100 mm Hg
- Weight gain from baseline
    - ≥ 5% - < 10% increase
    - ≥ 10% - < 20% increase
    - ≥ 20% increase
- Weight loss from baseline
    - ≥ 5% - < 10% decrease
    - ≥ 10% - < 20% decrease
    - ≥ 20% decrease

The derived visit window definitions for vital signs are displayed in Table 6.

Table 6. Analysis Window Definitions for Vital Signs Results

Visit	Nominal Day	Range
Baseline	1 (first dose date)	[-14, 1]
Week 4	28	[2, 55]
Week 12	84	[56, 111]
Week 24	168	[112, 195]
Week 36	252	[196, 279]
Week 48	336	[280, 363]
⋮	⋮	⋮
Week XX	XX times 7	[(Week XX-1 upper range + 1, (XX times 7) + 27]
EOT	Last dose date	[Last dose date, Last dose date + 15]
30 days post EOT	Last dose date + 30 days	[Last dose date + 16,]

13.3.4 PHYSICAL EXAMINATIONS

Physical examination information will be provided in a subject listing and include at minimum: subject id, treatment arm, visit, assessment date, physical examination, results and clinical findings (if applicable).

13.3.5 SUPPLEMENTAL PROCEDURES

Procedures received from the first day of treatment to the last day of treatment will be summarized by SOC class and preferred term.

13.3.6 PROGRESSIVE DISEASE

Progressive disease information will be presented in a subject listing and include at minimum: subject id, age, treatment arm, assessment date, splenic progression status, progression date, form of splenic progression (increase in splenic volume of >=25% from baseline, splenectomy or other splenic surgery, splenic irradiation), leukemic transformation status, transformation date, form of leukemic transformation (peripheral blood blast >=20% sustained for 8 weeks, bone marrow blast >=20%) and treatment end date.

13.3.7 SUBGROUP ANALYSIS OF SAFETY

If there are enough patients per group, treatment-emergent adverse events, including all AEs, grade 3/4 AEs, and SAEs, and hematology toxicity may also be summarized by subgroups as appropriate. Subgroups may include, but are not limited to, baseline platelet count ($\leq$ 50,000/μL vs. > 50,000/μL) and baseline hemoglobin (< 100 g/L vs. $\geq$ 100 g/L).

14 GENETIC BACKGROUND

Details of the genetic background analysis can be found in the DNA analysis plan.

15 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Details of the PK/PD analysis can be found in the PK/PD analysis plan.

16 DETERMINATION OF SAMPLE SIZE

The determination of sample size for this dosage finding study was driven by a targeted predictive probability (see Table 3) and to ensure adequate precision to evaluate efficacy using percent reduction of spleen volume from baseline. Based on past clinical experience (e.g., ≤10% SVR

deemed as the minimally, clinically meaningful reduction), variance in percent reduction in spleen volume (standard deviation ≈ 20%) from PERSIST-1 and PERSIST-2 studies, and the need for exploratory modeling analysis of pacritinib dose-response and dose-exposure-response relationship, a maximum of 30 evaluable patients per treatment arm are adequate to evaluate efficacy.

As for safety, with a sample size of 30 patients per arm, if the true incidence rate for a specified safety event is 5% among patients per each arm, then the chance of observing at least 1 event among 30 patients will be 78%. At the end of the study, if none of the 30 patients in each treatment arm experience an AE, then the true incidence rate of the AE is no greater than 5.2% with 80% confidence and no greater than 7.4% with 90% confidence.

A 15% overage will be built into the study sample size to account for potential drop-outs, thus a maximum of 35 patients are planned for enrollment per treatment arm.

17 DATA HANDLING RULES

17.1 Definition of Baseline Value

The baseline value for safety analyses will be defined as the last assessment prior to the start of treatment, unless otherwise specified.

17.2 Partial Current MF Diagnosis Date

For patients who have a partial diagnosis date, the 15th of the month will be used if day is missing, and July 15th will be used if both the month and day are missing.

17.3 Partial or Missing AE Onset and Resolution Dates

For AE summaries, the missing day of onset of an adverse event will conservatively be set to:

- First day of the month that the AE occurred if this is after the date of the start of first treatment.
- One day after the first treatment if this is the same month that the AE occurred.
- The 15th of the month and year if the AE month and year are before the month and year of the first treatment.

If the onset date of an adverse event is missing both day and month, it will be set to:

- January 1 of the year of onset, as long as this is after the first study treatment.
- One day after the first study treatment if this is the same year that the AE occurred.
- July 1st of the year if the AE year is before the year of the first study treatment.

If the day of resolution of an adverse event is missing, it will conservatively be set to the last day of the month or 30 days after the last dose of study treatment if this day is in the same month and year,

whichever is earlier. If the day of resolution of an adverse event is missing both day and month, it will conservatively be set to the last day of the year or 30 days after the last dose of study treatment if this day is in the same year, whichever is earlier.

All missing and partial dates will be presented "as is" in listings.

17.4 Partial or Missing Transfusion Dates

For transfusion summaries, the missing day of transfusion start date will conservatively be set to:

- First day of the month that the transfusion occurred if this is after the date of the start of first treatment.
- One day after the first treatment if this is the same month that the transfusion occurred.
- The 15th of the month and year if the transfusion month and year are before the month and year of the first treatment.

If the onset date of the transfusion is missing both day and month, it will be set to:

- January 1 of the year of onset, as long as this is after the first study treatment.
- One day after the first study treatment if this is the same year that the transfusion occurred.
- July 1st of the year if the transfusion year is before the year of the first study treatment.

If the day of resolution of transfusion is missing, it will conservatively be set to the last day of the month or 30 days after the last dose of study treatment if this day is in the same month and year, whichever is earlier. If the day of resolution of transfusion is missing both day and month, it will conservatively be set to the last day of the year or 30 days after the last dose of study treatment if this day is in the same year, whichever is earlier.

All missing and partial dates will be presented "as is" in listings.

17.5 Partial or Missing Concomitant Medication and Supplemental Procedure Dates

For concomitant medication, when missing the start date information the following imputation will be applied:

Derive data only with the missing day of the month:

- First day of the month that the CM occurred if this is after the date of the start of first treatment.
- One day after the first treatment if this is the same month that the CM occurred.
- The 15th of the month and year if the CM month and year are before the month and year of the first treatment.

Derive data if both day and month are missing:

- January 1 of the year of onset, as long as this is after the first study treatment.
- One day after the first study treatment if this is the same year that the AE occurred.
- July 15th of the year if the CM year is before the year of the first study treatment.

When missing the end date information the following imputation will be applied:

Derive data only with the missing day of the month:

- Set as the last day of the month

Derive data with both missing day and month:

- set as December 31th

All missing and partial dates will be presented "as is" in listings

12.1 Analysis Windows

Analysis windows will be defined as follows:

Endpoint	Nominal Visit	Nominal Study Day	Analysis Windows (in days)
Spleen volume (SPV)	Week 12	84	(63 to 105)
	Week 24	168	(147 to 189)
	Week 36	+3 months pos-24 week	+/- 21 days
	…		
Total Symptom Score (TSS)	Week 12	84	(63 to 105)
	Week 24	168	(147 to 189)
	Week 36	+3 months pos-24 week	+/- 21 days
	…		
Patient Global Impression Assessment (PGIC)	Week 12	84	(63 to 105)
	Week 24	168	(147 to 189)
	Week 36	+3 months pos-24 week	+/- 21 days
	…		

12.2 Laboratory Results Reported as a Range

Laboratory results that are reported as less than or greater than a certain value (limit of quantification) or as a range of values will be imputed for analysis using the rules described below.

Myeloblast Percentages

- Myeloblast results in the hematology data reported as <X% will be imputed with the value (X-1)% for analysis.
- Myeloblast results in the hematology data reported as ≤X% will be imputed with the value X% for analysis.
- Myeloblast results in the hematology data reported as X-Y% will be imputed with the value Y% for analysis.

Other Laboratory Results

- Laboratory results reported as <X will be imputed with the value (X-1) for analysis. Results reported as <X.Y will be imputed by subtracting one from the last significant digit (Y). Results reported as <0.1 will be imputed as 0 for analysis as long as the normal range extends to 0.
- Laboratory results reported as >X will be imputed with the value (X+1) for analysis. Results reported as >X.Y will be imputed by adding one to the last significant digit (Y).

13 REFERENCES

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