Statistical Analysis Plan

SAP Version:	Version 5.0
Date of SAP Version	May 27, 2020
Sponsor:	Rigel Pharmaceuticals, Inc. 1180 Veterans Boulevard South San Francisco, CA 94080, USA
Study Title:	A Phase 3 Open Label Extension Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura
Drug Name:	Tavalisse® (Fostamatinib Disodium)
Protocol Number:	C-935788-049
EudraCT Number:	2013-005454-30
Protocol Version/Date:	Final Protocol Version 5.0, dated November 19, 2019
Author:	[redacted] Director of Biostatistics Rigel Pharmaceuticals, Inc.

APPROVAL SHEET

Product:	Fostamatinib Disodium
Protocol Number:	C-935788-049
EudraCT Number:	2013-005454-30
Version:	Version 5.0
Version Date:	May 27, 2020

The undersigned have reviewed this statistical analysis plan and find it to be consistent with the protocol as it applies to their respective areas.

Approver	Signature	Date
[redacted] Executive Director of Biometrics Rigel Pharmaceuticals, Inc.		
[redacted] Vice President Clinical Science and Safety Rigel Pharmaceuticals, Inc		

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse Event
AIHA	Autoimmune Hemolytic Anemia
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Counts
ANOVA	Analysis of variance
AST	Aspartate Aminotransferase
bid	*bis in die* (twice daily)
BP	Blood Pressure
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue Scale
FDA	Food and Drug Administration
GCP	Good clinical practice
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgG	Immunoglobulin G
IRB	Institutional Review Board
ITP	Immune Thrombocytopenic Purpura
IV	Intravenous
IVIg	Intravenous IgG
kg	Kilogram
KPS	Karnofsky Performance Status
L	Liter
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LS	Least Square
mg	Milligram

Abbreviation	Definition
PK	Pharmacokinetic
PP	Per Protocol
qd	*quaque die* (once daily)
RTX	Rituximab
R406	Rigel compound R940406
R788	Rigel compound R935788 (fostamatinib)
RBC	Red blood cell
SAE	Serious Adverse Event
Syk	Spleen Tyrosine Kinase
TEAE	Treatment Emergent Adverse Event
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
wAIHA	Warm Autoimmune Hemolytic Anemia
WBC	White Blood Cell
WHO	World Health Organization

1.0 INTRODUCTION

This document details the analysis plan for the study entitled "A Phase 3 Open Label Extension Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura". It describes the proposed efficacy and safety analyses, including planned summary tables and by-subject data listings.

Immune Thrombocytopenic Purpura (ITP) is a disorder manifested by immune mediated platelet destruction. It is estimated that there are 50–100 new cases per million persons each year in the U.S. and Europe, with the cases roughly divided between adults and children. The natural history of the disease in children is different and generally more benign than ITP in adults. ITP may be primary or secondary to a variety of conditions, including autoimmune disease (e.g., Systemic Lupus Erythematosus), lymphoid malignancies, or chronic viral diseases such as hepatitis and HIV.

ITP in adults is typically a chronic disease, with a low spontaneous remission rate. Although responses to glucocorticoids, intravenous IgG (IVIg), splenectomy, and thrombopoietic agents may be encouraging, a significant number of patients remain severely thrombocytopenic for long durations and are subject to risk of spontaneous or trauma-induced hemorrhage. Even in asymptomatic patients, platelet counts below 20,000/μL - 30,000/μL often prompt treatment.

Fcγ receptor (FcγR) signaling in monocytes and macrophages plays an important role in the initiation and propagation of autoimmune responses. The activating FcγR are associated with a signaling subunit, referred to as the FcRγ chain, whose phosphorylation subsequent to receptor activation results in the recruitment and activation of spleen tyrosine kinase (Syk). Syk is an important component of the signaling system of activated Fc receptors, as well as the B-cell receptor (BCR).

Aggregation of the Fc receptors, induced by antibody-antigen complexes, can induce a multitude of cellular functions (including degranulation, arachidonic acid metabolism, antibody dependent cellular cytotoxicity, phagocytosis and cytokine secretion) depending on the cell type, and leads to tissue damage and the propagation of inflammatory responses. FcγR have been implicated in immune destruction of platelets. Accelerated clearance of circulating IgG-coated platelets via Fcγ receptor (FcγR)-bearing macrophages in the spleen and liver is a key mechanism in ITP. Fostamatinib (R788), the prodrug of R406, is a potent and relatively selective inhibitor of Syk and consequently of the FcR and BCR signaling pathways. Fostamatinib inhibits Syk and FcR signaling at concentrations generally achieved with doses of 100 mg twice daily (*bid*) and above, and both preclinical and early clinical data have affirmed its activity in ITP.

Additional details of the program are described in the Protocol.

2.0 STUDY OBJECTIVES

The primary objective of this study is to assess the long-term safety of fostamatinib in subjects with persistent/chronic ITP.

The secondary objectives of this study are:

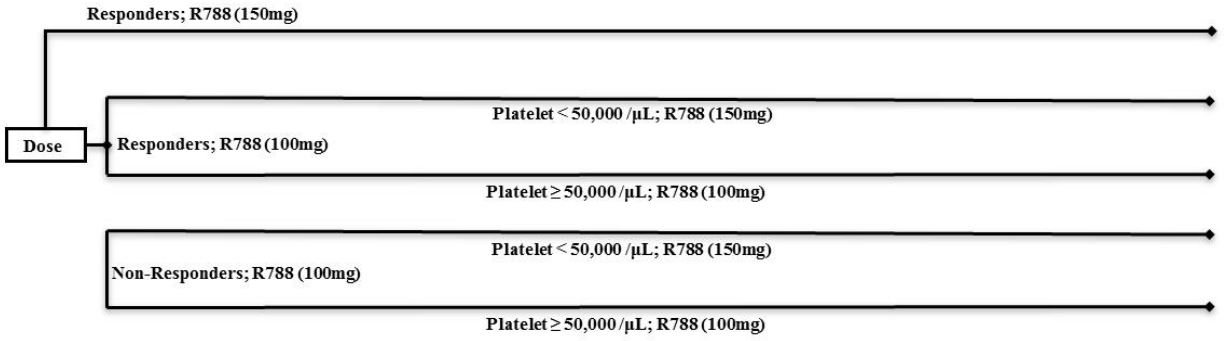
- To establish the long-term efficacy of fostamatinib in achieving and maintaining a stable platelet count in subjects who complete the treatment phase of Study C-935788-047 or Study C-935788-048
- To assess the pharmacokinetic (PK) profile of fostamatinib in subjects with persistent/chronic ITP.

3.0 INVESTIGATIONAL PLAN

3.1. Overall Study Design Summary

This is a Phase 3 multi-center, open label extension study to evaluate the long-term safety and efficacy of fostamatinib in achieving and maintaining a stable platelet response in subjects with persistent/chronic Immune Thrombocytopenic Purpura (ITP). For the purpose of this study, the term 'subject' will refer to patients with persistent/chronic ITP participating in this study. Up to 150 subjects will be enrolled at multiple sites. The study will consist of monthly visits for 18 months followed by every-other-month visits for a maximum of 5 years of treatment or until commercial availability of drug, whichever comes first.

Figure 1: Study Design



*At Month 1 subjects receiving fostamatinib 100 mg *bid* should have the dose escalated to fostamatinib 150 mg *bid* if the platelet count is <50,000/µL.

Eligible subjects include subjects from Study C-935788-047 or C-935788-048 who have completed the Week 24 evaluation or who discontinue early (starting at Week 12) due to lack of response. Subjects must meet the Inclusion/Exclusion criteria listed in Section 6.1 and Section 6.2 of the protocol to be eligible to participate in the study. Subjects designated as responders (defined as platelet count ≥ 50,000/µL) at the time of rollover will continue in the extension study at their current Study C-935788-047 or C-935788-048 dose and regimen. Subjects who

enter the extension study as non-responders (defined as platelet count < 50,000/μL) will be allocated to fostamatinib 100 mg PO bid regardless of their dose and regimen in the prior study. All subjects will receive open-label fostamatinib. Subjects will remain blinded to their treatment assignment (active or placebo) from Study C-935788-047 or C-935788-048.

At Month 1, subjects receiving fostamatinib 100 mg PO *bid* should have the dose escalated to fostamatinib 150 mg PO *bid* if platelet count < 50,000/μL and the study drug is well tolerated (refer to Section 7.2.1 of the protocol). Conversely, the dose may be reduced at any time to a dose as low as fostamatinib 100 mg PO *qd* if dose limiting AEs are observed as defined by the extension study protocol (see Section 7.2.2 and Appendix 1, Appendix 2, Appendix 3, and Appendix 4 of the protocol).

A schedule of study procedures for this study is presented in **Table 1.**

Table 1: Schedule of Study Procedures

	Day 1 Screen/ Enrollment[a]	End of Month 1 (± 3 days)	Months 2–18 (± 3 days)	Months 19–60 (± 1 week)	Follow-up (± 7 days)[i]
Informed consent	X				
Inclusion/Exclusion	X				
Physical exam/KPS	X	X	monthly	every other month	X
Concomitant medications	X	X	monthly	every other month	X
Vital signs[b]	X	X	monthly	every other month	X
Bleeding assessment[c]	X	X	monthly	every other month	X
ECG	X				
Hematology[d]	X		monthly	every other month	X
Platelets	X	X	monthly	every other month	X
Serum chemistries (including LFTs)[e]	X		Months 4, 8, 12, 16	every other month	X
LFTs only[f]			monthly (in months full serum chemistries not done)		X
Immunoglobulin levels	X				X
Urinalysis	X		Months 4, 8, 12, 16	every 4 months	X
Urine pregnancy test[g]	X		every other month	every other month	
SF-36[h]	X		Month 12		
AEs	X	X	monthly	every other month	X
PK			Month 2		
Study drug dispensed/Accountability	X	X	monthly	every other month	
Dose adjustment (prn)	X	X	monthly	every other month	

a. **Screen/Enrollment (Day 1):** These procedures are equivalent to Week 24 visit of Study C-935788-047 or C-935788-048; assessments performed as part of Week 24 may be used to assess subject's eligibility to roll over and do not need to be repeated specific to Study C-935788-049.
b **Vital Signs:** blood pressure, pulse and temperature
c **Bleeding assessment:** IBLS scale only; prior to Version 4, protocol used both IBLS and WHO bleeding scales
d **Hematology:** CBC with differential, RBC, hemoglobin, hematocrit, MCHC, MCH, MCV, MPV, RDW, reticulocytes
e **Serum chemistries:** Na, K, Cl, bicarbonate (CO2), Ca, PO4, BUN, creatinine, globulin, glucose, LDH, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin
f **LFTs:** ALT, AST, ALP, LDH, and bilirubin (total and direct)
g **Pregnancy Test**: For women of childbearing potential, regardless of birth control methodology
h **SF-36:** At visits where the SF-36 is evaluated the SF-36 must be the first assessment performed.
I **Follow-up visit:** to be completed approximately 2 weeks (+/- 7 days) after subject's last treatment or at the time of early treatment termination.

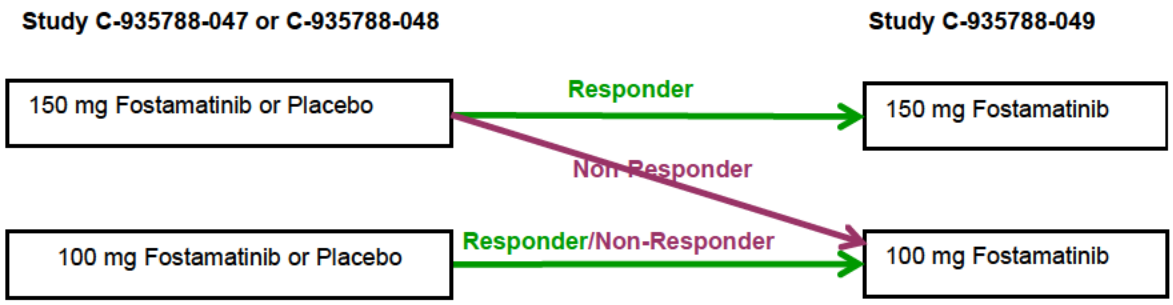
3.2. Methods of Assigning Subjects to Treatment

Depending on their response to treatment in Study C-935788-047 or C-935788-048, subjects will receive fostamatinib as follows(see Figure 2):

- Responders will initiate open-label fostamatinib treatment with the dose and regimen that was efficacious in achieving a stable platelet response in Study C-935788-047 or C-935788-048.
- Non-responders will initiate treatment with fostamatinib 100 mg PO *bid*. If a non-responding subject has previously required a dose reduction (to less than 100 mg PO *bid*) due to an adverse event, the Sponsor's Medical Monitor should be contacted regarding the subject's eligibility and the appropriate starting dose.

Subjects will self-administer the study drug throughout the 24-month treatment period. Subjects on a *bid* dosing regimen will self-administer 1 tablet twice-a-day by mouth: once in the morning and once in the evening at least 8 hours apart. Subjects on a *qd* dosing regimen will self-administer 1 tablet per day by mouth in the morning.

Figure 2: Initial Treatment Allocation



3.3. Blinding

This is an open label study, so no blinding will be done. However, subjects will remain blinded to their treatment assignment (active or placebo) from the previous study.

3.4. Determination of Sample Size

No sample size calculations were performed for this study. The sample size will be based upon the number of patients in the C-935788-047 and C-935788-048 studies who are eligible to participate in this study and choose to participate.

3.5. Changes to the Protocol-Specified Analyses

For the method of assigning subject to treatment (as mentioned in Section 3.2), protocol states that the responders will initiate open-label fostamatinib treatment with the dose and regimen that was efficacious in achieving a stable platelet response in Study C-935788-047 or C-935788-048. In reality, the patients were not required to be stable responders but rather to have at least one platelet count of at least 50,000/μL.

The protocol defines the baseline value as the last measurement for the corresponding variable prior to the first randomized dose at Visit 3 in Study C-935788-047 or C-935788-048. For the analyses described by this SAP, the baseline value will be defined as the last measurement for the corresponding variable prior to the first dose of fostamatinib in Study C-935788-047 or C-935788-048 (for fostamatinib patients in the previous study) or the present study (for placebo patients in the previous study), unless specified otherwise in the SAP.

For secondary efficacy endpoint, duration of stable platelet response, has been changed to duration of platelet response, the protocol specified that subjects who drop out of the study before achieving a platelet response will be assigned duration of platelet response of 0 and will be censored. In addition to the duration of platelet response, total duration of platelet response is also defined in **Section 4.4** in this SAP and will be analyzed.

For secondary efficacy endpoint, subjects with reduction in the dose of concomitant ITP therapy while maintaining an adequate platelet count (yes/no), the protocol states that a two-sided, McNemar's test was to be performed to compare the proportions of subjects achieving a reduction in the dose of concomitant ITP therapy while maintaining an adequate platelet count between the fostamatinib and placebo treatments. In this SAP, no McNemar's test will be performed, instead the patient level of listing for the concomitant ITP therapy using during the present study will be provided in data listing.

Also, per protocol version 5, one-sample t-test was to be used to evaluate the mean change from baseline for each post-baseline time point for the safety endpoints of systolic and diastolic blood

pressure, liver function test [i.e., ALT, AST, alkaline phosphatase, and bilirubin (total, direct, and indirect)] and ANC. This one-sample t-test will not be performed.

Interventions required to manage hypertension will also be summarized by baseline use of anti-hypertensives.

The additional exploratory efficacy endpoints and other endpoints are defined in **Appendix 14.1**.

The additional other endpoints for SF-36 are presented as follows:

- Patients with change from baseline ≥ 8 at Month 12 for each of 8 SF-36 domains (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health), respectively(yes/no)
- Patients with change from baseline ≥ 8 for physical health summary score and mental health summary score, respectively(yes/no)

4.0 EFFICACY, SAFETY AND PHARMACOKINETIC ENDPOINTS AND DEFINITIONS

4.1. Demographic Characteristics

Demographic characteristics include the following:

- Age (years)
- Age Category (years): < 50, 50 – <65, and ≥ 65
- Age Category (years): 65 - <75, and ≥ 75 (this age category is only for patients with age ≥ 65 years old)
- Gender
- Ethnicity
- Race
- Weight (kg)
- Weight Category (kg): <65, 65 -< 80, 80 - <90 and ≥ 90
- Height (cm)
- Body Mass Index (BMI) (kg/m^2)
- Body Mass Index BMI Category (kg/m^2): <18.5, 18.5 -<30 and ≥ 30

Demographic characteristics above are defined the same way as those in Study C-935788-047 or C-935788-048 baseline.

4.2. ITP History and Previous ITP Procedures

ITP history, previous ITP procedures, and baseline characteristics include the followings:

- Baseline Platelet count(/uL)
- Baseline IBLS scores and baseline WHO Bleeding Scale scores
- Previous Splenectomy (Yes/No)
- Duration of ITP (years)
- Type of prior ITP (Persistent ITP or Chronic ITP)

- Prior ITP therapies
- Number of unique prior ITP therapies

Baseline Platelet count(/uL) is defined as last measurement prior to the first dose of fostamatinib, either the first dose of fostamatinib in Study C-935788-047 or C-935788-048 (for fostamatinib patients in the previous study) or the present study (for placebo patients in the previous study).

Baseline IBLS scores and baseline WHO Bleeding Scale scores, previous splenectomy (Yes/No), duration of ITP (years), type of prior ITP (Persistent ITP or Chronic ITP), prior ITP therapies and the number of unique prior ITP therapies are defined in the same way as presented for Study C-935788-047 or C-935788-048.

4.3. Primary Efficacy Endpoint

Version 1: The first version of the primary efficacy endpoint is for the purpose of assessing efficacy among all patients while they are on active treatment in one of the prior studies, in the current extension study, or in both. This version of the primary efficacy endpoint is the achievement and maintenance of a stable platelet response defined as follows:

1) Achievement of a platelet count of at least 50,000/μL within 12 weeks of beginning active treatment and

2) Achievement of a sustained stable platelet response; defined as no two visits, at least 4 weeks apart, with a platelet count < 50,000/ μL, without an intervening visit with a platelet count of ≥ 50,000/ μL unrelated to rescue therapy, within a period of 12 months following initial achievement of the target platelet count (see above).

The beginning of active treatment may be in the prior study or in the present extension study, depending upon when the patient first received active treatment. Patients who discontinue treatment due to lack of efficacy or to an AE prior to 12 months following achievement of a platelet count of at least 50,000/μL will be considered failures.

Version 2: The second version of the primary efficacy endpoint is for the purpose of a within-patient, between-study comparison of fostamatinib and placebo among patients randomized to placebo in either of the prior studies, This version of the primary efficacy endpoint is the achievement and maintenance of a stable platelet response defined as follows:

1) Achievement of a platelet count of at least 50,000/μL within 12 weeks of beginning treatment (placebo treatment in the prior study and fostamatinib treatment in the present study) and

2) Achievement of a sustained stable platelet response; defined as no two visits, at least 4 weeks apart, with a platelet count < 50,000/ μL, without an intervening visit with a platelet count of ≥ 50,000/ μL unrelated to rescue therapy, within a period of 12 weeks following initial achievement of the target platelet count (see above).

Platelet counts taken within 28 days of rescue therapy will be excluded when determining the value of this endpoint. Patients who discontinue treatment or patients who are rescued prior to 12 weeks following achievement of a platelet count of at least 50,000/μL, will be considered failures.

4.4. Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- The duration of platelet response (months) and total duration of platelet response (months)
- Patients with reduction in the dose of concomitant ITP therapy while maintaining an adequate platelet count (yes/no)

Duration of platelet response will be defined as the length of time from when the patient first achieves a platelet count of at least 50,000/μL until the first of two visits with platelet counts < 50,000/μL that are at least 4 weeks apart without an intervening visit with a platelet count ≥ 50,000/μL unrelated to rescue therapy.

Four additional definitions of duration of platelet responses are stated in **Appendix 14.2**

Patients who drop out of the study before achieving a platelet response (i.e., achieving a platelet count of ≥ 50,000/μL will be assigned a value of 0 for this endpoint. Patients who drop out of the study by the time of database lock while still maintaining a platelet response will be censored as of the time of the last platelet measurement prior to dropping out of the study. Similarly, patients who remain in the study by the time of database lock while still maintaining a platelet response will be censored as of the time of the last platelet measurement prior to the time of database lock. For patients who have achieved and are maintaining a platelet response but who have discontinued treatment due to lack of efficacy or to an AE by the time of database lock, duration of platelet response will be defined as the time from first achieving a platelet count of ≥ 50,000/μL until discontinuation of treatment.

The total duration of platelet response is defined as the sum of all durations of platelet responses.

Regarding the secondary efficacy endpoint of patients with reduction in the dose of concomitant ITP therapy while maintaining an adequate platelet (yes/no), a patient is said to have reduction while maintaining an adequate platelet count if the date of reduction of dose of concomitant ITP therapy occurs within the span of the duration of a platelet response during the C-935788-049 study and the reduction was not prompted by AE.

4.5. Safety Endpoints

The following safety endpoints will be evaluated:

- Adverse events
- Adverse events of interest, including:

- Gastrointestinal (GI) events
    - Nausea
    - Vomiting,
    - Diarrhea as reported by SMQ (v19.1) of non-infectious diarrhea
    - Abdominal pain
- Infection
- Hypertension as reported by SMQ (v19.1)
- Increases in transaminases and/or total bilirubin as defined by SMQ (v19.1) of Hepatic Disorder
- Neutropenia

- Percent change from baseline in lab assessments (hematology, serum chemistry and liver function tests) over time
- Presence of abnormal changes from baseline in laboratory values per Common Terminology Criteria for Adverse Events (CTCAE) criteria V 5.0 (e.g., hematology, chemistry)
- Severity of bleeding according to the IBLS and the WHO bleeding scale
- Change from baseline in vital signs (i.e., systolic /diastolic blood pressures, pulse, temperature) over time
- Post baseline blood pressure categorized based on post baseline systolic and diastolic blood pressure values.

4.6. Other Endpoints

- Change and percent change from baseline in Karnofsky Performance Status (KPS) over time
- Change from baseline in Short form-36 (SF-36) over time

4.7. Pharmacokinetic Endpoints

Characterization of the PK profile of R406 (the active metabolite of fostamatinib) including Cmax, AUC, and Tmax in a subset of subjects with ITP.

5.0 STATISTICAL METHODS

5.1. General Considerations

The statistical analysis for this study will be performed using SAS® version 9.4 or higher. All one-sided statistical tests will be performed at the 0.025 significance level, and all two-sided tests will be performed at the 0.05 significance level, unless otherwise indicated.

Prior study treatment group will refer to the patient's randomized treatment group (fostamatinib or placebo) from the previous study in which the patient participated. Unless otherwise specified.

Analyses will be based on only the data from the present study (C935788-049), except for the baseline value and a few other exceptions (e.g., duration of platelet response, primary efficacy endpoint, and the platelet count by-visit summary.

Data collected in this study will be documented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, 25th percentile (Q1), 75th percentile (Q3), standard deviation, minimum and maximum. Categorical variables will be summarized using frequencies and percentages.

Data listings will be sorted by prior study treatment group and patient ID number. All date fields will be presented in a format of ddmmmyyyy (i.e., 01Jan2014) in the listings. All data will be included in the data listings.

As a global note, platelet counts taken within 28 days of rescue therapy will be excluded from any platelet count related analyses.

5.2. Adjustments for Covariates

No adjustments for covariates will be made.

5.3. Handling of Dropouts and Missing Data

No imputation will be performed for missing data

5.4. Interim Analyses and Data Monitoring

An interim analysis was performed for purposes of inclusion in the New Drug Application for fostamatinib.

5.5. Multicenter Study

This is a multicenter study. Up to 150 patients will be enrolled at multiple sites. No adjustments for site will be made in the statistical analyses.

5.6. Multiple Comparisons / Multiplicity

No adjustments for multiple comparisons/multiplicity will be made.

5.7. Examination of Subgroups

Platelet count will be summarized by 047/048 primary efficacy endpoint responder status and 049 primary efficacy endpoint version 2 responder status for 047/048 placebo patients, and for 049 primary efficacy endpoint **Version 1** responders (defined in **Section 4.3**).

Maximum systolic and diastolic blood pressure on active treatment (post-baseline of the present study) will be summarized by baseline use of anti-hypertensives.

Interventions required to manage hypertension will also be summarized by baseline use of anti-hypertensives and by prior study treatment group (fostamatinib and placebo) and overall.

5.8. Definition of Baseline Measurements

For the summary of baseline characteristics of present study, the baseline characteristics used for summary are defined in **Section 4.1** and **4.2**.

For the calculation of change from baseline, the baseline value is defined as the last measurement for the corresponding variable prior to the first dose of fostamatinib in Study C-935788-047 or C-935788-048 (for fostamatinib patients in the previous study) or the present study (for placebo patients in the previous study).

6.0 ANALYSIS POPULATIONS

6.1. Treated Population

The Treated Population will include all enrolled and treated patients in the present study. All efficacy and safety analyses will be performed on the Treated Population.

7.0 PATIENT DISPOSITION

The number of patients signing the informed consent, screen failures, and patients in the Treated Population will be presented. The numbers and percentages of patients who discontinued from the study at the time of database lock, along with the reason for discontinuation, will be also be presented.

8.0 DEMOGRAPHIC, BASELINE CHARACTERISTICS, ITP HISTORY AND PREVIOUS PROCEDURES

The demographic/baseline characteristics and ITP history/previous procedures are defined in **Section 4.1** and **4.2,** respectively. Descriptive statistics will be presented for the continuous variables. Frequencies and percentages will be presented for the categorical variables.

9.0 STUDY DRUG DISPENSING, COMPLIANCE, AND EXPOSURE

The dose level of fostamatinib dispensed and changes in the dose level dispensed will be summarized by visit using counts and percentages. Changes in the dose level dispensed include increase in dose level dispensed and decrease in dose level dispensed, respectively as follows:

- Increase in dose level dispensed, including change from 100 mg bid to 150 mg bid, change from 150 mg qd to 100 mg bid and change from 100 mg qd to150 mg qd, respectively
- Decrease in dose level dispensed including change from 150 mg bid to 100 mg bid, change from 100 mg bid to 150 mg qd and change from 150 mg qd to 100 mg qd, respectively

The expected number of doses, actual number of doses, number of missed doses, and percent compliance will be summarized by time interval and overall using descriptive statistics. Percent compliance is defined as the actual number of doses (tablets) the patient took during the time period divided by the total number of tablets expected to be taken, multiplied by 100.

The duration of dosing of fostamatinib and the mean total daily dose will be summarized using descriptive statistics and displayed in waterfall plots. In addition, the number and percentage of following subgroups of patients will be presented

- Patients with at least 3 months of duration of dosing of fostamatinib
- Patients with at least 6 months of duration of dosing of fostamatinib
- Patients with at least 12 months of duration of dosing of fostamatinib
- Patients with at least 18 months of duration of dosing of fostamatinib
- Patients with at least 24 months of duration of dosing of fostamatinib

The number and percentage of patients with at least one dose interruption with duration less than or equal to 2 days, greater than 2 days, and of unknown duration, and the number and percent of patients with a dose interruption followed by early termination, with at least one dose interruption due to adverse events, and with any dose interruption will be presented. Among patients with at least one dose interruption, the total number and mean number per patient of dose interruptions with duration less than or equal to 2 days, greater than 2 days, and of unknown duration, and the total number and mean number per patient of dose interruptions due to adverse events will be presented.

10.0 EFFICACY ANALYSES

10.1 Primary Efficacy Endpoint

10.1.1 Version 1

The first version of the primary efficacy endpoint is defined in **Section 4.4** and applies for all patients entering C-935788-049 study. It will be summarized using counts and percentages, together with a 95% exact (Clopper-Pearson) confidence interval for the true percentage of Version 1 responders.

10.1.2 Version 2

The second version of the primary efficacy endpoint is defined in **Section 4.4** and applies for all patients randomized to placebo in either C-935788-047 or C-935788-048 studies and entering C-935788-049 study.

These endpoints will be summarized based on a shift table (**Table 3** below) presenting shifts in responder status from placebo treatment in the C-935788-047 or C-935788-048 studies to fostamatinib treatment in the C-935788-049 study using counts and percentages, together with 95% exact (Clopper-Pearson) confidence intervals for the true percentage of Version 2 responders. In addition, the following hypothesis test will be conducted:

H_0: $P_{01} - P_{10} = 0$ vs. H_a: $P_{01} - P_{10} \neq 0$,

Where P_{01} denotes true proportions of non-responders from placebo patients in C-935788-047 or C-935788-048 studies who become Version 2 responders in C-935788-049 study and

P_{10} denotes true proportions of stable responders from placebo patients in C-935788-047 or C-935788-048 studies who become Version 2 non-responders in C-935788-049 study.

here P_{01} and P_{10} are estimated by $\frac{c}{a+b+c+d}$ and $\frac{b}{a+b+c+d}$, respectively, where a, b, c and d are number of patients as defined in **Table 3** below

Table 3. Shift of Response Status For Version 2 Response

Placebo Patients in C-935788-047 or C-935788-048 Studies Who Entered C-935788-049 Study

		Version 2 Responders in C-935788-049 Study		
		Yes	No	Total
Stable Responder in C-935788-047 or C-935788-048 Studies	Yes	a	b	a+b
	No	c	d	c+d
	Total	a+c	b+d	a+b+c+d

The p-value of the null hypothesis test for H_0: $P_{01} - P_{10} = 0$ will be calculated using a 2-sided exact McNemar's test with a significance level of 0.05. The 95% confidence intervals for the difference in proportion of $P_{01} - P_{10}$ will be calculated using normal approximation method.

10.2 Secondary Efficacy Endpoint

The secondary efficacy endpoints are as follows:

10.2.1 Duration of Platelet Response

Duration of platelet response is defined in **Section 4.4.** It will be analyzed using the Kaplan-Meier method, and the Kaplan-Meier estimate of the median duration of platelet response will be presented together with the 95% confidence interval for the true median. The descriptive summary for the duration of platelet response will also be presented with number (n) of patients with non-missing duration of platelet response and mean/ standard deviation (SD)/ 25th percentile/ median/ 75th percentile/ minimum/maximum of duration of platelet response.

In addition, the duration of platelet response will also be analyzed for the following subgroups of patients:

- C-935788-047 or C-935788-048 fostamatinib subjects who were C-935788-049 primary efficacy endpoint version 1 responders
- all C-935788-049 primary efficacy endpoint version 1 responders
- C-935788-047 or C-935788-048 placebo patients who were C-935788-049 primary efficacy endpoint version 2 responders.

The same analyses as mentioned above will be conducted for the duration of platelet response based on the additional definitions as mentioned in **Appendix 14.2.**

10.2.2 Total Duration of Platelet Response

The total duration of platelet response is defined in **Section 4.4** and will be analyzed in the similar way as duration of platelet response as mentioned in **Section 10.2.1** .

The same analyses as mentioned above will be conducted for the total duration of platelet response based on the additional definitions as mentioned in **Appendix 14.2.**

10.2.3 Reduction in the Dose of Concomitant ITP Therapy

This endpoint is defined in **Section 4.4**. The patient level listing of concomitant ITP use during the present study will be provided.

10.3 Additional Efficacy Analyses

Platelet count will be summarized by scheduled visit using descriptive statistics. Platelet count will also be summarized by

- Study C-935788-047/C-935788-048 primary efficacy endpoint responder status,

- Study C-935788-047/C-935788-048 primary efficacy endpoint responder status and C-935788-049 primary efficacy version 2 responder status. This is for C-935788-047/C-935788-048 placebo patients entering C-935788-049 study
- For study C-935788-049 primary efficacy endpoint version 1 responders. This is for all C-935788-047/C-935788-048 patients entering C-935788-049 study

The summaries above will be performed by prior study treatment group in C-935788-047/ C-935788-048 studies and overall.

For each of exploratory efficacy endpoints mentioned in **Appendix 14.1,** frequencies and percentages of patients achieving the endpoint (Yes) will be provided.

11.0 SAFETY ANALYSES

The safety endpoints of this study are defined in **Section 4.5.**

11.1 Adverse Events

Analyses of adverse events (AEs) will include all adverse events in the present study, not just treatment emergent AEs (e.g., if a placebo patient has an AE starting in C-935788-047/C-935788-048 studies and continuing in the present study, this AE will be included in the analyses) . Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 19.1). The number of events and the number and percentage of patients with at least 1 adverse event, at least one severe AE, at least one moderate or severe AE, at least 1 serious adverse event (SAE), at least 1 treatment related adverse event, at least one adverse event leading to dose reduction, at least one adverse event leading to dose interruption, at least one adverse event leading to drug withdrawal, and at least one adverse event leading to death will be presented. AEs that are possibly or probably related to study treatment, or for which the relationship to study treatment is missing, will be considered treatment related. Among patients with at least one AE, the mean number of AEs per patient will also be presented. The number and percentage of patients with adverse events of interest [any gastrointestinal (GI) complaints (nausea, vomiting, diarrhea, abdominal pain), overall and separately, infection, hypertension, neutropenia, transaminase elevation, and bilirubin elevation] will be presented. For the AEs of nausea, vomiting, abdominal pain, and infection, Rigel will specify preferred terms that fit into these categories. AEs, SAEs, AEs of interest, AEs leading to dose reduction, AEs leading to dose interruption, AEs leading to drug withdrawal, and AEs leading to death will be summarized at the patient level by MedDRA system organ class (SOC) and preferred term using frequencies and percentages. AEs will also be tabulated at the event level and the patient level by severity

and by causal relationship to study drug. AEs of interest will be tabulated at the event level and the patient level by severity.

Regarding diarrhea (as reported by SMQ 19.1), the following additional analyses will be performed:

- A patient's maximum diarrhea severity grade for the post-baseline period will be summarized using counts and percentages.
- A patient level of listing for diarrhea that include the diarrhea severity grade, diarrhea start and end dates and duration of diarrhea in the present study will be provided.

11.2 Clinical Laboratory Tests

Descriptive statistics will be presented by scheduled visit for the actual values and the changes and percentage changes from baseline for each selected quantitative laboratory test (hematology, serum chemistry, and liver function test). Actual values of categorical urinalysis test results will be summarized by scheduled visit. Lab values that are out of normal range will be flagged in the data listings.

Box plots indicating mean and median as well as the 25th and 75th percentiles, reference plots, and spaghetti plots will be presented by study scheduled visit for both raw values and changes from baseline.

Descriptive statistics for the actual values, changes from baseline, and maximum value observed post baseline will be presented by scheduled visit in the present study. In addition, two types of shift tables based on lab values classified per Common Terminology Criteria for Adverse Events (CTCAE) Grade Version 5.0 will be provided as follows:

- Grades based on baseline lab values vs. the grades based on the worst post-baseline lab values observed in the present study,
- Grades based on baseline lab values vs. the grades based on the last post-baseline lab value observed in the present study.

These two types of shift table summaries above will be applied to the following selected lab parameters, respectively:

- Liver function tests (i.e., ALT, AST, total bilirubin and indirect bilirubin)
- Absolute neutrophil count (ANC)
- Alkaline Phosphatase

Regarding lab values of ALT, the following additional analyses will be performed:

- Descriptive statistics for the average number of events of lab value increasing from baseline for each patient.

- Frequencies and percentages for number of patients with the events of lab value increasing from baseline

Same additional analyses will be performed for AST.

11.3 Vital Signs

Descriptive statistics will be presented by scheduled visit for the actual values and the changes and percentage changes from baseline for each vital sign. The maximum post baseline systolic blood pressure categories (< 140 mmHg, 140 - < 160 mmHg, 160 - <180 mmHg and ≥ 180 mmHg) will be summarized using counts and percentages. This analysis will also be performed by baseline use of anti-hypertensives (yes/no). The anti-hypertensives are the medications with any of the following ATC codes at baseline: C02 (anti-hypertensives), C03 (diuretics), C04 (peripheral vasodilators), C07 (beta blocking agents), C08 (calcium channel blockers), and C09 (agents acting on the rennin-angiotensin system). These analyses will be repeated for maximum post baseline diastolic blood pressure categories (< 90 mmHg, 90 - < 100 mmHg, 100 - <110 mmHg and ≥ 110 mmHg).

The number and percentage of following types of patients will be presented:

- Patients with systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg at consecutive visits (2 or more visits, 3 or more visits) of present study
- Patients with systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg anytime during the post-baseline of present study
- Patients with systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg at consecutive visits (2 or more visits, 3 or more visits) of present study
- Patients with systolic BP ≥ 160 mmHg or diastolic BP ≥ 100 mmHg anytime during the post-baseline of present study
- Patients with systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg at consecutive visits (2 or more visits, 3 or more visits) of present study
- Patients with systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg anytime during the post-baseline of present study

In addition, shifts based on new guidance in blood pressure (**Appendix 14.3**) from normal, elevated, Stage 1, Stage 2 and hypertensive crisis at baseline to normal, elevated, Stage 1, Stage 2 and hypertensive crisis for the maximum observed value, and the last value post baseline will

be tabulated. The maximum observed blood pressure and the last blood pressure post baseline will be based on both scheduled and unscheduled visits.

Box plots indicating mean and median as well as the 25th and 75th percentiles, reference plots, and spaghetti plots will be presented by scheduled visit for both raw values and changes from baseline.

11.4 IBLS and WHO Bleeding Scale Scores

The IBLS will be analyzed as follows:

- The mean of the IBLS scores across 9 anatomical sites and across visits during the 24-month treatment period in present study will be summarized using descriptive statistics.
- The highest IBLS score across the 9 anatomical sites and the total IBLS score will be summarized by visit.

The WHO bleeding scale will be analyzed as follows:

- The mean of the WHO bleeding scale across visits during the 24-month treatment period in present study will be summarized using descriptive statistics.

In addition, both IBLS bleeding scale and WHO bleeding scale analyses mentioned above will be performed by prior study treatment group and overall.

11.5 Physical Examination

Abnormal physical exam (PE) findings will be summarized by body system and visit using counts and percentages.

11.6 Karnofsky Performance Status (KPS)

Karnofsky Performance Status Scale results, both raw and change and percentage change from baseline, will be summarized by visit using descriptive statistics.

11.7 Concomitant Medications

Concomitant medications (non-ITP) and ITP concomitant medications will be summarized at the patient level by World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) class 3 and preferred term using counts and percentages.

12.0 OTHER ANALYSES

12.1 Pharmacokinetics

A separate document will describe the analyses of pharmacokinetic data.

12.2 SF-36

Descriptive statistics will be presented by scheduled visit for the actual values and the changes from baseline for the following:

- Eight domains: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health, respectively
- Two summary scores: physical health summary and mental health summary, respectively
- Proportions of patients with change from baseline ≥ 8 at month 12 for each domain and summary score, respectively, will be presented

12.4 Protocol Deviations

Protocol deviations will be maintained in the trial master file and will be listed and discussed in the clinical study report.

12.5 Rescue Therapy

A rescue therapy event is defined based on the medication administration start date. Two or more rescue medications started on the same day are counted as one rescue therapy event. Only rescue medications administered on or after the first dose of study drug in the present study are included.

The number of rescue therapy events per patient will be summarized using descriptive statistics for the following:

- Placebo patients of the C-935788-047/C-935788-048 study who received rescue therapy prior to Week 10 (Day 73)
- Placebo patients of the C-935788-047/C-935788-048 study who received rescue therapy after Week 10

The number and percentage of patient who received any rescue therapy in the present study will be summarized for

- the placebo patients of the C-935788-047/C-935788-048 study who received rescue therapy prior to Week 10 (Day 73)
- the placebo patients of the C-935788-047/C-935788-048 study who received rescue therapy after Week 10,
- all patients in C-935788-049 study

In addition, the number of patients who received any rescue therapy will be summarized using counts and percentages, and the number of rescue therapy events per patient for all patients who

received any rescue therapy will be summarized using descriptive statistics. These analyses above will be conducted by prior study treatment group and overall.

13.0 REFERENCES

Whelton, et al., Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, American College of Cardiology, 2017

14.0 APPENDICES

14.1 Additional Exploratory Efficacy Endpoints and Other Endpoints

14.2 Additional Definitions of Duration of Platelet Response and Total Duration of Platelet Response

The additional definitions of duration of platelet responses are presented as follows:

1) The length of time from when the patient first achieves a platelet count of at least 50,000/μL until the loss of platelet response, which is defined as the earlier time of (the first of two consecutive visits with platelet counts < 30,000/μL that are at least 4 weeks apart or the first use of rescue therapy after first achieving a platelet count of at least 50,000/μL)
2) The length of time from when the patient first achieves a platelet count of at least 50,000/μL until the loss of platelet response, which is defined as the earlier time of (the first of two consecutive visits with platelet counts < 20,000/μL that are at least 4 weeks apart or the first use of rescue therapy after first achieving a platelet count of at least 50,000/μL)
3) The length of time from when the patient first achieves a platelet count of at least 30,000/μL until the loss of platelet response, which is defined as the earlier time of (the first of two consecutive visits with platelet counts < 30,000/μL that are at least 4 weeks apart or the first use of rescue therapy after first achieving a platelet count of at least 30,000/μL)
4) The length of time from when the patient first achieves a platelet count of at least 30,000/μL until the loss of platelet response, which is defined as the earlier time of (the first of two consecutive visits with platelet counts < 20,000/μL that are at least 4 weeks apart or the first use of rescue therapy after first achieving a platelet count of at least 30,000/μL)

Patients who drop out of the study before achieving a platelet response [i.e., achieving a platelet count of ≥ 50,000/μL for definition 1)-2) or ≥ 30,000/μL for definitions 3) - 4)] will be assigned a value of 0 for this endpoint. Patients who drop out of the study by the time of database lock while still maintaining a platelet response will be censored as of the time of the last platelet measurement prior to drop out of study respectively. Similarly, patients who remain in the study by the time of database lock while still maintaining a platelet response will be censored as of the time of the last platelet measurement prior to the time of database lock. For patients who have achieved and are maintaining a platelet response but who have discontinued treatment due to lack of efficacy or to an AE by the time of database lock, duration of platelet response will be defined as the time from first achieving a platelet response [i.e., achieving a platelet count of ≥ 50,000/μL for definition 1)-2) or ≥ 30,000/μL for definitions 3)- 4)] until discontinuation of treatment.

For each of additional definitions of duration of platelet responses 1)-4) above, the total duration of platelet response will be defined as the sum of all durations of platelet responses.

14.3 New Categories of Blood Pressure in Adults

The following new blood pressure (BP) categories is based on 2017 Guideline (see Section 13.0) for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

BP Categories	**Systolic BP (SBP)**		**Diastolic BP (DBP)**
Normal	< 120 mmHg	and	< 80 mmHg
Elevated	120 – 129 mmHg	and	< 80 mmHg
Stage 1	130 – 139 mmHg	or	80 – 89 mmHg
Stage 2	≥ 140 mmHg	or	≥ 90 mmHg
Hypertensive Crisis	Higher than 180 mmHg	or	Higher than 120 mmHg

Note: Individuals with SBP and DBP in 2 categories should be designated to the higher BP category.