Certain information within this clinical study report has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

This may include, but is not limited to, redaction of the following:

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- Patient identifiers within the text, tables, or figures or in by-patient data listings.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
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CLINICAL PROTOCOL

A Phase 3 Open Label Extension Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura

Protocol Number: C-935788-049

EudraCT Number: 2013-005454-30

Study Sponsor: Rigel Pharmaceuticals, Inc.
1180 Veterans Boulevard
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Sponsor Representative: [redacted]

Version 1.0: 18 December 2013
Version 2.0: 08 April 2014
Version 3.0: 21 November 2014
Version 4.0: 8 November 2016
Version 5.0 11 November 2019

Sponsor Signature for Protocol C-935788-049

I certify that I have the authority to approve this protocol on behalf of the Sponsor, Rigel Pharmaceuticals, Inc. The study will be conducted in accordance with this protocol and all applicable national and international laws, rules, and regulations including the principles of Good Clinical Practice (GCP), the Declaration of Helsinki, and regulations of the United States Food and Drug Administration (FDA).

[redacted]

11-NOV-2019

Date

[redacted]
Vice President Clinical Sciences and Drug Safety
Rigel Pharmaceuticals, Inc.

Signature of Agreement for Clinical Protocol C-935788-049

I agree to the following:

- To conduct the study in strict accordance with this protocol and the contract with the Sponsor, Rigel Pharmaceuticals, Inc., (Rigel), and all applicable national and international laws, rules, and regulations, including the principles of Good Clinical Practice, the Declaration of Helsinki, and the regulations of the United States FDA.
- To maintain adequate and accurate records and to make those records available for inspection by Rigel (or its authorized representative), the FDA, or any other Regulatory Agency authorized by law.
- To report to Rigel (or its authorized representative) any adverse events (AEs) or serious AEs (SAEs) that occur in the course of the study, as specified in the protocol.
- To promptly report to the Institutional Review Board/Independent Ethics Committee (IRB/IEC) and Rigel all changes in research activity and all unanticipated problems involving risks to subjects or others and not make any changes in the protocol without approval from Rigel and the IRB/IEC, except when necessary to eliminate hazards to the subjects.
- To personally conduct or supervise the study, and ensure that all associates, colleagues, and employees assisting in the conduct of the study are also duly qualified, have adequate understanding of the study, are informed about their obligations and commitments, and are provided adequate training on how to conduct their delegated tasks.
- To ensure that the IRB/IEC responsible for initial and continuing review and approval of this study complies with applicable laws and that the requirements for obtaining informed consent and IRB/IEC review and approval are met.
- To comply with all other requirements regarding the obligations of Investigators as described in this protocol and in applicable laws.
- That this protocol and all data and information generated in connection with this study are the exclusive property of Rigel.

I have read and understood the Investigator's Brochure, including potential risks and side effects of the study drug.

I represent that I am a licensed medical practitioner in good standing under applicable law and that I am qualified and duly authorized to conduct the study. I acknowledge that Rigel has the right to terminate the study at any time.

Investigator's Signature	**Date**

Print Investigator's Name and Title

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1.0 PROTOCOL SYNOPSIS

Name of Finished Product(s):	Fostamatinib Disodium (R935788)

Title of Study: A Phase 3 Open Label Extension Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura (ITP)

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, and to assess the pharmacokinetic (PK) profile of fostamatinib in subjects with persistent/chronic ITP.

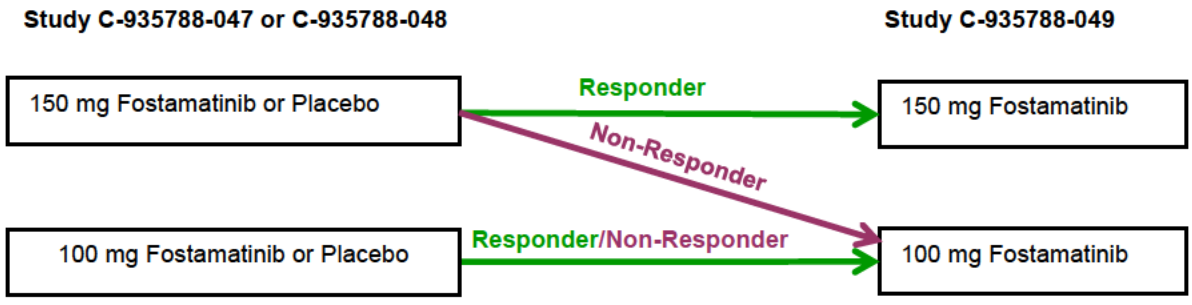
Methodology:

This is a Phase 3 multicenter, open-label extension study to evaluate the long-term safety and the efficacy of fostamatinib in achieving and maintaining a stable platelet response in subjects with persistent/chronic ITP. The study will consist of monthly visits for 18 months followed by every-other-month visits for a maximum treatment duration of 5 years or until commercial availability of drug, whichever comes first.

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. All subjects will receive open-label fostamatinib.

Subjects designated as responders (defined as platelet count ≥ 50,000/μL) at the time of rollover will continue at their current dose and regimen in the extension study. Subjects who enter the extension study as nonresponders (defined as platelet count < 50,000/μL) will be allocated to fostamatinib 100 mg PO *bid* regardless of their dose and regimen in Study C-935788-047 or C-935788-048. Subjects will remain blinded to their treatment assignment in Study C-935788-047 or C-935788-048 (active or placebo).

Treatment Allocation



Subjects may continue to receive the concomitant medications for ITP that were allowed in the prior study (ie, glucocorticoids at dose less than equivalent of 20 mg prednisone daily, azathioprine or danazol). Subjects in whom the platelet count is stable at ≥ 50,000/µL may have the dose of concomitant medications for ITP gradually reduced according to standard practice.

At the end of Month 1 (approximately Day 30), 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). 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 this protocol.

Certain therapeutic regimens for ITP will be permitted for subjects with platelet counts < 50,000/µL who need "rescue" support of the platelet count. Allowed therapeutic regimens include:

- IVIg: up to 1 g/kg x 1-3 days, or
- IV anti-D: up to 50-75 µg/kg x 1-2 days, or
- IV methylprednisolone up to 1 g/day x 1-3 days or oral dexamethasone up to 40 mg/day x 1-2 days or oral prednisone up to 1 mg/kg/day x 1-3 days.

At Month 2, blood samples for PK analysis will be collected from a subset of 12 subjects at selected sites. Subjects will remain at the clinic for up to 9 hours during the visit. When a subject arrives at the clinic, the time of the last dose of fostamatinib will be recorded in the eCRF.

Samples (4 mL) of whole blood will be collected at the following time points: predose and 0.5, 1, 2, 4, 6, and 8 hours post-dose.

Number of Subjects: Up to 150 subjects will be enrolled at multiple sites.

Study Population: Patients with persistent/chronic ITP. For the purpose of this study, the term 'subject' will refer to patients with persistent/chronic ITP participating in this study.

Inclusion Criteria:

1. Subject must be willing and able to give written informed consent by signing an IRB-approved Informed Consent Form prior to participating in any study-specific procedures.

2. Subjects must have completed the Week 24 evaluation of Study C-935788-047 or C-935788-048 or have discontinued early (starting at Week 12) due to lack of response. No more than 7 days may have elapsed between the last day of treatment on Study C-935788-047 or C-935788-048 and the initial dosing (Day 1) in Study C-935788-049.

3. Male or female at least 18 years of age.

4. Females must be either post-menopausal for at least 1 year or surgically sterile; or if female of child-bearing potential, must not be pregnant or lactating and must agree to use an acceptable method of birth control throughout the duration of the trial and for 30 days following the last dose. Acceptable methods of birth control are defined as: hormonal contraception (pill, injection or implant) used consistently for at least 30 days prior to enrollment, intrauterine device (IUD), double-barrier (ie, condom and spermicide, or condom and diaphragm), or complete abstinence.

5. In the Investigator's opinion, the subject has the ability to understand the nature of the study and any hazards of participation and to communicate satisfactorily with the Investigator.

Exclusion Criteria:

1. Any subject who discontinued participation in Study C-935788-047 or C-935788-048 prior to Week 12 or for any reason other than lack of response. Exceptions may be considered on a case-by-case basis after consultation between the Investigator and Sponsor with the specific reason for the exception noted.

2. Subjects with poorly controlled hypertension during Study C-935788-047 or C-935788-048, defined as persistent or repeated systolic ≥ 140 mmHg, or diastolic ≥ 90 mmHg whether or not the subject is receiving anti-hypertensive treatment.

3. Subjects with the following laboratory abnormalities at the time of enrollment (Day 1): a leukocyte count < 2,000/μL, a neutrophil count (ANC) of < 1,000/μL, lymphocyte count < 750/μL, Hgb < 10 g/dL, or transaminase levels (ALT, AST) > 1.5 x ULN, bilirubin > 1.5 x ULN, or estimated glomerular filtration rate (eGFR) < 30 mL/min.

4. Subjects who have a significant infection, an acute infection such as influenza, or known inflammatory process at the time of enrollment into this study.

5. Subjects who have received any blood or blood products within the 2 weeks prior to enrollment (IVIg or anti-D are allowed if used for rescue therapy).

Investigational Product: Fostamatinib disodium (R935788) 100 mg and 150 mg tablets

Route of Administration: Oral

Dose: The initial dose will be 100 mg fostamatinib PO *bid* daily.

At the end of Month 1, subjects who have initiated dosing at fostamatinib 100 mg PO *bid* in this extension study (and who have not previously had a dose reduction) should have their dose increased to fostamatinib 150 mg PO *bid* if the platelet count remains below 50,000/μL and the study drug has been well tolerated.

Treatment with fostamatinib has been associated with adverse events (AEs) that may require temporary interruption of the study drug and/or a reduction in study drug dose. Modification of study drug administration may be required.

Duration of Treatment: A maximum of 5 years or until fostamatinib becomes commercially available, whichever comes first.

Statistical Methods:

Analysis Populations:

a. Treated Population

The Treated population will include all enrolled and treated subjects. All efficacy endpoints will be analyzed based on the Treated population, and subjects will be analyzed according to their actual treatment. The efficacy analyses based on the Treated population will be considered the primary efficacy analyses. All analyses of safety will also be performed on the Treated Population.

b. Per-Protocol Population

The Per-Protocol (PP) population will include all subjects in the Treated population who had no major protocol violations in either study

All efficacy endpoints will also be analyzed based on the PP population, and subjects will be analyzed according to their actual treatment. The analyses based on the PP population will be considered secondary analyses of efficacy.

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 count defined as follows:

1) Achievement of a platelet count of at least 50,000/μL within 12 weeks of beginning active treatment.
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 subject first received active treatment. Subjects 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. This endpoint will be summarized using counts and percentages, together with a 95% exact (Clopper-Pearson) confidence interval (CI) for the true percentage.

Version 2: The second version of the primary efficacy endpoint is for the purpose of a within-subject, between-study comparison of fostamatinib and placebo among subjects 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 count 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).

Subjects who discontinue treatment due to lack of efficacy or to an AE prior to 12 weeks following achievement of a platelet count of at least 50,000/μL, will be considered failures. The null and alternative hypotheses for the comparison of fostamatinib vs. placebo are as follows:

$$H_0: p_F = p_P \quad \text{vs.} \quad H_1: p_F \neq p_P$$

where p_F and p_P denote the true proportions achieving and maintaining a stable platelet count for fostamatinib and placebo, respectively. The null hypothesis will be tested using a 2-sided McNemar's test conducted with a significance level of 0.05.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints are as follows:

- Duration of stable platelet response.
- Proportion of subjects in whom a reduction in the dose of concomitant ITP therapy can be achieved while maintaining an adequate platelet count.

The duration of stable platelet response will be analyzed using the Kaplan-Meier method, and the Kaplan-Meier estimate of the median duration of stable platelet response will be presented together with the 95% CI for the true median.

Achieving a reduction in the dose of concomitant ITP therapy while maintaining an adequate platelet count will be summarized using counts and percentages and a 95% exact (Clopper-Pearson) CI for the true percentage. A two-sided, McNemar's test will be performed to compare the proportions of successes between the fostamatinib and placebo treatments.

Safety Endpoints:

The safety outcomes of this study include the frequency and severity of bleeding according to the IBLS, the change from baseline in blood pressure, liver function, and ANC; the incidence of GI complaints; infection; and overall AEs.

Pharmacokinetic Endpoints:

Pharmacokinetic parameters to be estimated for the major metabolite R406 include maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the plasma concentration-time curve through 8 hours ($AUC_{(0-8)}$). C_{max} and T_{max} will be taken directly from the data;

$AUC_{(0-8)}$ will be calculated using the linear trapezoidal method. These PK parameters will be summarized using descriptive statistics.

Determination of Sample Size:

The sample size will be based upon the number of subjects in the C-935788-047 and C-935788-048 studies who are eligible to participate in this study and who choose to participate.

2.0 ABBREVIATIONS AND TERMS

ADP	Adenosine Diphosphate
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
ANC	Absolute Neutrophil Counts
Anti-D IgG	Anti-Rho (D) immunoglobulin
APLA	Antiphospholipid antibodies
AST	Aspartate aminotransferase
AUC	Area under the curve
BCR	B-cell receptor
BCRP	Breast cancer resistant protein
bid	twice daily
BP	Blood pressure
CBC	Complete blood counts
CFR	United States Code of Federal Regulations
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
CRO	Contract Research Organization
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
FcR	Fc receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
h	hour
HIPAA	Health Insurance Portability and Accountability Act
IBLS	Immune Thrombocytopenic Purpura Bleeding Score
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

Ig	Immunoglobulin
IgG	Immunoglobulin G
INR/aPTT	International Normalized Ratio/Activated Partial Thromboplastin Time
IRB	Institutional Review Board
ISI	International sensitivity index
ITP	Immune Thrombocytopenic Purpura
ITT	Intent-to-treat
IV	Intravenous
IVIg	Intravenous IgG
IWRS	Interactive web response system
KPS	Karnofsky Performance Status
LFT	Liver function tests
OATP	Organic anion transporter
PD	Pharmacodynamic
P-gp	P-glycoprotein
PK	Pharmacokinetic
PO	by mouth
PP	Per protocol
qd	once daily
R406	Rigel compound R940406 (the major metabolite of R788)
R788	Rigel compound R935788 (fostamatinib)
RA	Rheumatoid arthritis
RBC	Red blood cell
SAE	Serious adverse event
SF-36	Short form-36
SOP	Standard operating procedure
SRC	Safety Review Committee
Syk	Spleen tyrosine kinase
T_{max}	Time of maximum plasma concentration
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization

3.0 INTRODUCTION

3.1 Background

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 among 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 (ie, systemic lupus erythematosis), 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 kinase 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.

3.2 Nonclinical Studies

Bussel et al reported on a preclinical study with a R788/R406 in a murine model of ITP. [(1)] Mice injected with an antibody directed to a platelet βII integrin (anti-CD41) were thrombocytopenic (70% reduction) when platelets were enumerated 24 hours post injection. Mice treated with 25 or 40 mg/kg R788 were partially protected from the antibody-induced thrombocytopenia. Mice treated with vehicle alone displayed no protection. To confirm this work, Rigel embarked on a similar study of antibody-induced thrombocytopenia. Genetically identical inbred C57BL/6 mice and genetically heterogeneous CD-1 outbred mice were pretreated with vehicle or 20, 40, or 80 mg/kg R788 and dosed at 4-8 hour intervals for the duration of the study. Drug administration was initiated at various times prior to and following injection of platelet-depleting antibody (anti-CD41) or isotype control antibody. Whole blood was collected, and platelet

counts determined at 2 time points, (8 or 24 hours), following administration of depleting antibody.

Vehicle-treated C57BL/6 mice injected with CD41 antibody demonstrated uniform and significant platelet depletion at 8 hours post administration (350 x 10^3 platelets/μL whole blood in vehicle-treated mice, compared with 1,200 x10^3 platelets/μL in the isotype control mice, representing a 71% reduction in platelet count). Vehicle-treated CD-1 mice injected with anti-CD41 antibody also demonstrated uniform and significant platelet depletion at 8 hours post-antibody administration, showing a mean reduction of platelets to 33 x 10^3 platelets/μL whole blood, which is 2.4% of the isotype control-treated animal platelet count (1,376 x 10^3 platelets/μL). Significant prevention of platelet depletion was seen in both C57BL/6 ($p < 0.05$) and CD-1 ($p < 0.001$) strains of mice treated with the 80 mg/kg dose of fostamatinib (mean platelet counts of 651 x 10^3 platelets/μL whole blood and 280 x 10^3 platelets/μL, respectively). The platelet counts from both C57BL/6 and CD-1 mice treated with 20 or 40 mg/kg fostamatinib were not significantly different from those in vehicle-treated mice ($p > 0.05$).

In the absence of disease, fostamatinib/R406 had no effect on the time required for cessation of bleeding following an acute injury (tail nick). Wild-type (normal mice) treated with R406 at concentrations in excess of 15 μM, had no significant difference in bleeding time compared with untreated mice or mice treated with vehicle alone, while the active controls, treated with aspirin, had a significant prolongation of bleeding time.

3.3 Clinical Development of Fostamatinib in ITP

A Phase 2 pilot trial (Study C-935788-007) in adults with persistent/chronic ITP (defined as platelet count < 30,000/μL for ≥ 3 months) is ongoing (now as an investigator sponsored study). [(1)] All patients had failed at least 2 standard therapeutic regimens. Patients were treated with escalating doses of fostamatinib in cohorts of 3. After a cohort completed 4 weeks of treatment, a subsequent cohort could be initiated. Patients were required to complete 2 weeks at a given dose before the dose could be increased (by 25 mg *bid*). Dosing was initiated at 75 mg *bid* to 150 mg *bid*. Patients who responded, and then had their platelet counts decline, could have their dose further increased to a maximum of 175 mg *bid*. Eighteen patients entered the study and 2 patients remain on study.

In the twelve patients that responded to fostamatinib, the median platelet count increased from 16 x 10^9/L at baseline to a median peak of 105 x 10^9/L. Twelve patients achieved at least 1 substantial platelet increase, which was sustained in 8 patients. Patients with a sustained response had increased platelet counts on at least 67% of occasions, and experienced a reduced need for IVIg treatment or a tapering of steroids while on the study drug. The median dose of fostamatinib for the 8 patients with sustained response was 125 mg *bid*. Four patients had a transient response to fostamatinib however these patients continued to take study drug due to an improvement in clinical parameters such as bleeding, need for rescue medications, and ability to taper steroids. There appeared to be no clinical differences between responders and non-responders. [(1)]

Eighteen patients were included in the safety analysis during the initial treatment period. The 3 most commonly reported AEs were blood pressure increased (11 patients), petechiae

(10 patients), and aspartate aminotransferase increased (9 patients (61.1%, 55.6%, and 50.0%, respectively). Diarrhea was reported by 6 (33.3%) patients during the initial treatment period. Thirteen patients were included in the safety analysis during the responder extension period (treatment up to 24 months). The 5 most commonly reported AEs during this treatment period (experienced by all 8 patients) were blood glucose increased (10 patients), ecchymosis (9 patients), blood glucose decreased, blood pressure increased, and diarrhea (76.9%, 69.2%, 61.5%, respectively). An increase in aspartate transaminase (AST) was reported by 7 (53.8%) patients during the responder extension period. The transaminase increases were reported for any value greater than the upper limit of normal (ULN). Only 1 patient had a value 3 x ULN, and that patient had pre-existing autoimmune hepatitis.

3.4 Fostamatinib Safety and Pharmacokinetics

3.4.1 Single Ascending Dose Safety and Pharmacokinetics

R406, the major metabolite generated through the dephosphorylation of the prodrug R788 by intestinal phosphatases, appears rapidly in the systemic circulation after fostamatinib dosing, with median t_{max} ranging between 1 and 3 hours. Negligible levels of R788 are found in plasma. The terminal half-life of R406 ranges from 12 to 19 hours. Increasing the dose of fostamatinib tablets from 100 to 300 mg results in approximately dose-proportional increases in R406 exposure.

The geometric mean absolute bioavailability of R406 was estimated to be 54.6% (90% CI: 42.5 to 70.3%) in a bioavailability study in which 10 healthy volunteers were given a single oral dose of 150 mg fostamatinib and a 100 mcg intravenous (IV) dose of radiolabeled R406. Following the IV dose of R406 the volume of distribution at steady state (V_{ss}) was determined to be 256 L and total clearance (CL) of R406 was determined to be 15.7 L/h.

In healthy Japanese subjects, mean area under the curve (AUC) and maximum plasma concentration (C_{max}) were approximately dose-proportional between 50 and 200 mg single-doses. Following single-dose administration of fostamatinib 150 mg, higher C_{max} (~45% higher) and AUC (~27% higher) values were observed in Japanese subjects compared with white subjects (of European ethnicity), however, exposure in Japanese subjects generally tended to be comparable to other studies in which white subjects were enrolled.

3.4.2 Multiple-dose Pharmacokinetics

A 2- to 2.5-fold increase in R406 exposure (AUC) was seen at 160 mg *bid*, when Day 7 exposure was compared with Day 1. At 250 mg *bid*, a 3.3-fold increase in R406 AUC was observed on Days 7 and 20 over Day 1. The higher than unity accumulation ratio is, to a large extent, due to *bid* dosing for a compound with a relatively long half-life. A 3-fold increase in dose (from 100 to 300 mg *bid*) resulted in approximately 4-fold increase in steady-state exposure.

In Japanese healthy subjects, steady-state AUC and C_{max} were approximately dose-proportional between subjects administered 50 mg and 100 mg twice daily, and more than dose proportional between 100 mg and 200 mg twice daily based on comparison of data across Japanese and Western studies, R406 exposure was similar in Western and Japanese subjects with considerable overlap in exposure between groups.

It is worthwhile to note in the context of the single and multiple dose pharmacokinetic (PK) studies that platelet aggregation studies were performed and there was no effect on collagen or adenosine diphosphate (ADP) induced platelet aggregation at the highest doses tested.

3.4.3 Metabolism

The prodrug R788 is dephosphorylated in the intestinal mucosa to R406, the major metabolite, which in turn undergoes both oxidation and direct glucuronidation in humans. No unique metabolite was found in humans and there were no major circulating metabolites (> 10% of R406) in plasma. Renal elimination of parent drug was low.

3.4.4 Drug-Drug Interactions

3.4.4.1 Effect of Other Drugs on R406 Exposure

- A strong CYP3A4 inhibitor, ketoconazole, produced ~2-fold increase in exposure to R406, while a moderate inhibitor, verapamil, caused ~1.4-fold increase in R406 exposure. The magnitude of these interactions suggests that fostamatinib is not a sensitive CYP3A4 substrate and that there are alternate *in vivo* pathways of R406 metabolism in humans.

- A strong inducer of multiple CYP enzymes, rifampicin, decreased exposure to R406 to about 25% of that when fostamatinib is administered alone.

- Ranitidine, which increases gastric pH, did not have a clinically relevant effect on the PK of R406.

- Single doses of rosuvastatin and simvastatin did not have a clinically relevant effect on the PK of R406.

3.4.4.2 Effect of Fostamatinib on Exposure of Other Drugs

- R406 and R788 are substrates for and/or inhibitors of transporters (P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP)), cytochrome P450 (CYP3A4) and other enzymes (UGT1A1). R406 is a weak inhibitor of OATP1B1 *in vitro*, but this is predicted as unlikely to have relevant effects *in vivo*. Adverse findings in a mouse transgenic model suggested the possibility of an interaction between R406 and rosuvastatin resulting in increased plasma and liver rosuvastatin levels in an animal model sensitive to rosuvastatin. An analysis of serious AEs (SAEs) in the clinical safety database from the completed and ongoing fostamatinib Phase 2 - 3 clinical studies was conducted, focusing on patients concomitantly using a statin, including rosuvastatin. The analysis included data from 3048 patients in the long-term extension studies in rheumatoid arthritis (RA), as well as from the Phase 2 oncology program (studies in B- or T-cell lymphoma, diffuse large B-cell lymphoma, solid tumors and immune thrombocytopenia) up to 19th April 2012. In total, 389 patients were on a statin, (41 on rosuvastatin) while participating in a study. An analysis of SAEs did not reveal a new or emerging signal, nor did liver function differ from that observed in the general patient population. The body of

evidence from the safety profile in the clinic provides little evidence to suggest that there is a difference in the safety risk for patients on a statin.

- Digoxin geometric mean AUC_{ss} and $C_{max,ss}$ increased by 37% and 70%, respectively, when co-administered with fostamatinib. This increase in exposure is likely due to R788's inhibition of intestinal P-gp, resulting in an increase in the oral bioavailability of digoxin.

- The effect of fostamatinib on midazolam, a selective CYP3A4 substrate sensitive to interaction with CYP3A4 inhibitors, suggests that fostamatinib is a weak CYP3A4 inhibitor and clinically important interactions between fostamatinib and CYP3A4 substrates are unlikely.

- There appears to be an interaction between fostamatinib and ethinyl estradiol resulting in a modest increase in ethinyl estradiol exposure. There does not appear to be an interaction between fostamatinib and levonorgestrel.

- Fostamatinib did not affect the PK or pharmacodynamic (PD) of warfarin to a clinically relevant degree.

- Fostamatinib did not have a clinically relevant effect on the primarily CYP2C8 mediated metabolism of pioglitazone and does not appear to induce CYP2C8 *in vivo*.

3.4.4.3 Food Effect

A high-fat/calorie meal increased R406 AUC up to 23% with variable effects on C_{max} depending upon the formulation studied (-39% to +15%). This modest food effect is not considered clinically important.

3.5 Efficacy in Other Indications

To date, evidence of efficacy has been seen in open label Phase 2 studies in patients with B-cell lymphoma, in particular CLL. In 7 of the 8 completed randomized, blinded, and placebo-controlled Phase 2 and 3 RA trials, comprising over 3,000 patients, fostamatinib was effective in reducing joint tenderness and swelling and in improving functional outcome. The effective dose range was 100 to 150 mg *bid*. A lower dose (50 mg *bid*) was ineffective; the higher dose (150 mg *bid*) had more adverse effects without additional efficacy. In the 2 largest trials, no evident benefit on decreasing bone erosion or joint space narrowing was observed. For additional details, see Investigator Brochure.

3.6 Safety

A number of Phase 2 and 3 studies of fostamatinib have been conducted in several indications including ITP, RA and B- and T-cell lymphomas. Doses of fostamatinib have ranged from 50 to 250 mg PO *bid*, depending on the indication being treated. The majority of patients have been treated at doses ranging from 50-150 mg PO *bid*.

The overall pattern of adverse effects of fostamatinib in these various clinical settings (patients

with RA, severely ill patients with lymphoma and advanced solid tumors, chronically ill patients with ITP, and in healthy subjects), has been consistent, and includes dose-dependent effects on blood pressure (BP), ANC, dizziness, gastrointestinal (GI) complaints and liver function test abnormalities, all of which are reversible and manageable with appropriate safety monitoring (Table 1). The ITP patients (on no anti-metabolites or chemotherapy) have not manifested neutropenia, despite receiving higher doses of fostamatinib than the RA patients. The lymphoma patients have experienced more cytopenias, and infections, consistent with their extensive pre-treatment and underlying disease. In patients with solid tumors, the overall pattern of reported AEs was consistent with a population of heavily pretreated, relapsed patients with solid tumors of varying histologies.

Table 1: Frequent Adverse Events (Pooled Data - Phase 3 Placebo-Controlled RA Studies)

Sign/Symptom	Fostamatinib		Placebo
	100 mg *bid* **N = 723** **288 PY**	**100 mg *bid* (1 month) followed by 150 mg *qd*** **N = 710** **277 PY**	**N = 715** **254 PY**
BP > 140/90	333 (46%)	315 (44%)	170 (24%)
BP > 160/100	66 (9%)	63 (9%)	24 (3%)
Diarrhea	94 (33%)	112 (40%)	32 (13%)
Nausea	36 (13%)	41 (15%)	17 (7%)
Dizziness	18 (6%)	12 (4%)	5 (1%)
Abdominal Pain*	39 (14%)	38 (14%)	27 (11%)
ALT/AST ≥ 3 x ULN	38 (5%)	37 (5%)	17 (2%)
PMN < 1500/μL	66 (9%)	41 (6%)	8 (1%)

ALT= Alanine aminotransferase, AST = Aspartate aminotransferase, BP = Blood pressure, PY = Patient years, PMN = Polymorphonuclear leukocytes, ULN = Upper limit of normal

* Represents various verbatim terms

3.6.1 Blood Pressure Elevation

Blood pressure elevation, a well described adverse effect of treatment with fostamatinib, may reflect off-target inhibition of vascular endothelial growth factor receptor-2 (VEGFR-2).

In RA clinical trials, increases in blood pressure (mean ~2-4 mmHg) generally occurred early and were responsive to anti-hypertensive treatment. Patients with a history of hypertension appeared to be at greater risk of developing an increase in blood pressure and experienced higher mean increases (~5-9 mmHg). A few patients have experienced severe elevated blood pressure (≥ 180 systolic and ≥ 110 diastolic). In these studies the blood pressure effect has been reduced or eliminated over time by timely and effective anti-hypertensive treatment.

3.6.2 Liver Function Test Abnormalities

Mild to moderate increases in liver enzymes (ALT and AST) have been observed in

fostamatinib-treated patients. A very small number of patients have experienced elevations > 10 x ULN. Liver function test (LFT) abnormalities can occur at any time during the course of treatment. Mild increases in total and indirect bilirubin have also been observed in some fostamatinib treated patients and it has been determined that R406, the primary metabolite of fostamatinib, inhibits the enzyme UGT1A1 at fairly low concentrations (500 nM, concentrations regularly achieved clinically). While this effect is clinically innocuous, it requires consideration when interpreting liver function test results.

A total of 5 patients, three in Phase 2 and two in Phase 3 have met the Hy's law criteria for potential drug-induced liver injury. Two patients had alternative explanations for the abnormalities, one did not have simultaneous elevation of bilirubin and transaminases, and two patients had the UGT1A1*28 polymorphism upon genotyping.

3.6.3 Neutropenia

Dose-dependent decreases in ANC have been observed in the majority of studies with fostamatinib. Transient neutropenia (typically resolving within 5 to 7 days of discontinuation of fostamatinib) has been observed in RA patients receiving fostamatinib at doses ranging from 50 to 150 mg *bid*. Neutropenia was not observed to any significant degree in the Phase 2 ITP trial (although the experience was admittedly limited). Dose reduction has generally resulted in resolution of the neutropenia and permitted patients to remain on study drug for prolonged periods. To date, in the RA studies, there is no clear association between neutropenia and an increased risk of infection, and no evidence that treatment with fostamatinib increases the risk of opportunistic infection.

3.6.4 Gastrointestinal (GI) Effects

GI adverse effects have been reported in patients receiving fostamatinib. Diarrhea is the most commonly reported event and can generally be managed with loperamide and/or study drug interruption or dose reduction. Abdominal pain and nausea have also been among the commonly reported AEs.

There have been twelve SAE reports consistent with pancreatitis in the completed clinical trials. Factors confounding the ability to determine relationship to fostamatinib have included gall bladder disease, and other medications like antihypertensives and NSAIDs.

All but 1 episode resolved; this episode, in a patient with dyslipidemia who was using NSAIDs, had a fatal outcome. The relationship between fostamatinib and pancreatitis, if any, remains unclear.

3.6.5 Safety Summary

Fostamatinib has been extensively studied and a large safety database is available. Fostamatinib is generally well tolerated when administered at doses of 100-150 mg *bid*, as planned in the current study. The most common adverse effects observed with fostamatinib treatment include increased blood pressure, transaminase and bilirubin elevations, neutropenia, dizziness, and GI adverse effects such as diarrhea, nausea, vomiting and abdominal pain. For more information on the safety and activity of fostamatinib, see Investigators' Brochure.

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 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 C-935788-048, and to assess the PK profile of fostamatinib in subjects with persistent/chronic ITP.

4.2 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 count defined as follows:

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

2) Achievement of a sustained stable platelet response; defined as no 2 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)

Version 2: The second version of the primary efficacy endpoint is for the purpose of a within-subject, between-study comparison of fostamatinib and placebo among subjects 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 count 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 2 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)

4.3 Secondary Efficacy Endpoints

- The duration of any stable platelet response

- Proportion of subjects in whom a reduction in the dose of concomitant ITP therapy can be achieved while maintaining an adequate platelet count

4.4 Safety Endpoints

Safety endpoints include the frequency and severity of bleeding according to the IBLS; change from baseline (baseline value is the value at the initiation of active therapy) in blood pressure, liver function, and ANC; the incidence and severity of gastrointestinal (GI) effects (nausea, vomiting, diarrhea, abdominal pain); infection; and overall AEs.

4.5 Pharmacokinetic Endpoints

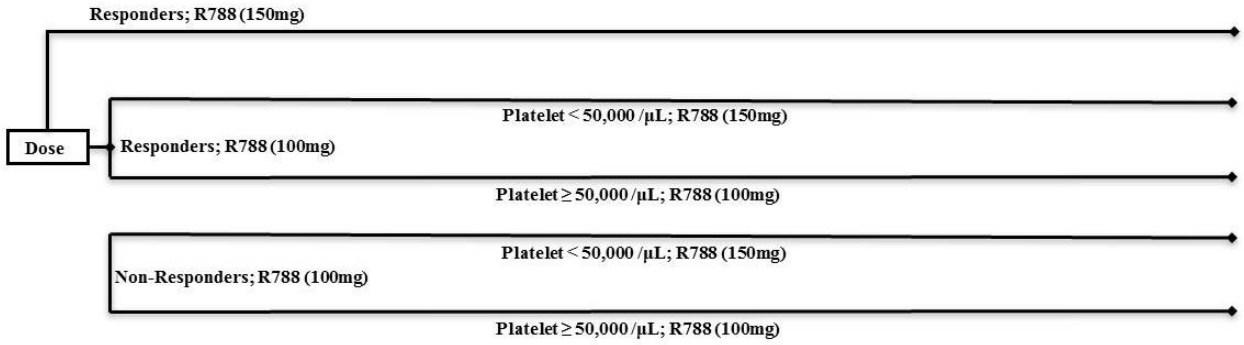
Characterization of the PK profile of R406 (the active metabolite of fostamatinib) including C_{max}, AUC, and T_{max} in a subset of subjects with ITP.

5.0 STUDY DESIGN

5.1 Summary of Study Description

This is a Phase 3 multicenter, open-label extension study to evaluate the long-term safety and the efficacy of fostamatinib in achieving and maintaining a stable platelet response in subjects with persistent/chronic 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).

Figure 1: Study Design



*At the end of 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 to be eligible to participate in the study. All subjects will receive open-label fostamatinib. 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 nonresponders (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. Subjects will remain blinded to their treatment assignment from Study C-935788-047 or C-935788-048 (active or placebo).

Subjects may continue to receive the concomitant medications for ITP that were allowed in the prior study (ie, glucocorticoids at a dose less than the equivalent of 20 mg prednisone daily, azathioprine or danazol). Subjects in whom the platelet count is stable at ≥ 50,000/µL may have the dose of concomitant medications for ITP gradually reduced according to standard practice.

At the end of Month 1 (approximately Day 30), 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). 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 this protocol (see Section 7.2.2 and Appendix 1, Appendix 2, Appendix 3, and Appendix 4.

5.2 Rationale for Proposed Dosing

Biomarker data from early studies of R940406 (R406), the active moiety of fostamatinib disodium, have demonstrated that the EC_{50} for its pharmacodynamic effects on the syk pathway was 496 ± 42.2 ng/mL (~1.06 µM), roughly equivalent to a daily AUC of ~ 12,000 ng•h/mL.

Phase 2 and 3 studies of fostamatinib in rheumatoid arthritis (RA), evaluated multiple dose levels including 50 mg PO *bid*, 100 mg PO *bid* and 150 mg PO *qd* or *bid*. Doses of 100 mg to 150 mg PO *bid* were effective in ameliorating the signs and symptoms of RA, while 50 mg PO *bid* was not effective. The average R406 exposure at 100 mg PO *bid* ranged from 4,400 to 7,020 ng•h/mL per dose interval, with daily exposures ranging from 8,800 to 14,000 ng•h/mL. These exposures are consistent with the levels needed to affect the syk pathway, as defined in biomarker assays, and support the 100 mg PO *bid* starting dose for this study.

Additionally, fostamatinib was previously studied in a small pilot trial of patients with ITP. Platelet counts improved in the majority of treated subjects, typically at doses ranging from 100-150 mg PO *bid*.

The purpose of this study is to confirm the long-term safety of fostamatinib and the beneficial effects on platelet counts in patients with persistent/chronic ITP.

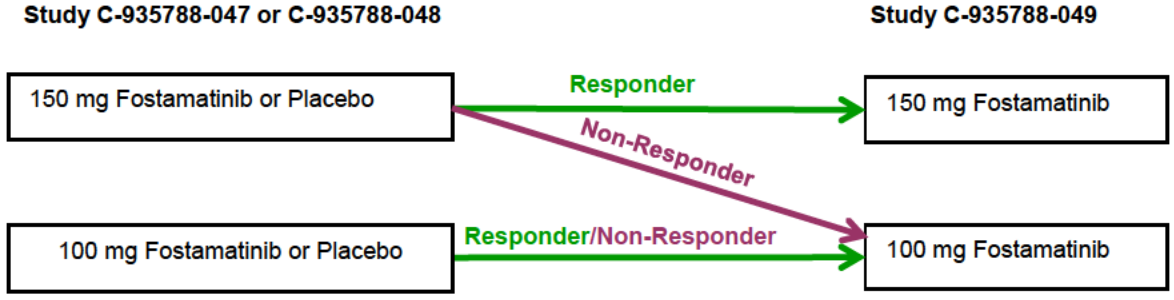
5.3 Study Treatment

Depending on their response to treatment in Study C-935788-047 or C-935788-048 there will be two categories of subjects in this study: responders and nonresponders (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.

- Nonresponders will initiate treatment with fostamatinib 100 mg PO *bid*. If a nonresponding subject has previously required a dose reduction (to less than 100 mg PO *bid*) due to an AE, the Sponsor's Medical Monitor should be contacted regarding the subject's eligibility and the appropriate starting dose.

Figure 2: Initial Treatment Allocation



Subjects will self-administer the study drug throughout the 60-month treatment period. Subjects on a *bid* dosing regimen will self-administer 1 tablet 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.

At the end of Month 1 (approximately Day 30), 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).

Subjects whose platelet count is consistently < 50,000/μL following 3 months (12 weeks) of treatment, and at least 4 weeks at a dose of 150 mg PO *bid* (provided this higher dose was tolerated), should be discontinued from the study, unless tangible clinical benefit for the use of fostamatinib is evident and the Sponsor agrees (all instances must be reviewed with the Sponsor's Medical Monitor). Examples of tangible clinical benefit may include, but are not limited to:

- Credible increase in platelet count (eg, increase in platelet count of at least 20,000/μL over initial baseline to a count ≥ 30,000/μL)
- Reduction in bleeding
- Reduction in the need for rescue therapy

5.3.1 IWRS

An Interactive Web Response System (IWRS) will be used to dispense the appropriate dose of fostamatinib to subjects in the study. The IWRS will assign a bottle number to each subject who is eligible for the open-label extension study.

5.4 Safety Monitoring

The Rigel Medical Monitor and representatives will closely monitor the safety of study drug on an ongoing basis by assessing reported AEs, vital signs, clinical laboratory values (hematology, serum chemistry, and urinalysis), and physical exams.

5.5 Safety Review Committee

An independent safety review committee (SRC) will also monitor safety throughout the study.

5.6 Administrative Structure

This trial is sponsored by Rigel. Up to 150 subjects will be enrolled at multiple sites.

A contract research organization (CRO) will be responsible for project management and team training, site identification and activation, site monitoring and management, data management, randomization code assignment, and writing and preparation of the final clinical study report. A second vendor will be responsible for biometrics. An additional CRO will be responsible for electronic trial master file preparation and maintenance. A financial services vendor will be used for clinical site contract negotiation and site payments, and collection of financial disclosure information. A safety CRO will be responsible for safety database set-up, data entry and maintenance, coding of SAE data and SAE case processing and preparation of expedited safety reports.

Data will be recorded directly in an electronic case report form (eCRF) via an electronic data capture (EDC) system. An IWRS will be used for study drug inventory management. Counting of platelets will be performed at the investigational institution or by local laboratories affiliated with the clinical sites enrolling subjects in the study. A central laboratory will be used for testing other routine laboratory parameters as well as biospecimen storage (see Section 7.6.6 for additional instruction).

6.0 SUBJECT SELECTION

6.1 Inclusion Criteria

1. Subject must be willing and able to give written informed consent by signing an IRB-approved Informed Consent Form prior to participating in any study-specific procedures.

2. Subjects must have completed the Week 24 evaluation of Study C-935788-047 or C-935788-048 or have discontinued early (starting at Week 12) due to lack of response. No more than 7 days may have elapsed between the last day of treatment on the Study C-935788-047 or C-935788-048 and initial dosing (Day 1) in Study C-935788-049.

3. Male or female at least 18 years of age.

4. Females must be either postmenopausal for at least 1 year or surgically sterile; or if female of child-bearing potential, must not be pregnant or lactating and must agree to use an acceptable method of birth control throughout the duration of the trial and for 30 days following the last dose. Acceptable methods of birth control are defined as: hormonal contraception (pill, injection or implant) used consistently for at least 30 days prior to enrollment, intrauterine device (IUD), double-barrier (ie, condom and spermicide, or condom and diaphragm), or complete abstinence.

5. In the Investigator's opinion, the subject has the ability to understand the nature of the study and any hazards of participation and to communicate satisfactorily with the Investigator.

6.2 Exclusion Criteria

1. Any subject who discontinued participation in Study C-935788-047 or C-935788-048 prior to Week 12 or for any reason other than lack of response. Exceptions may be considered on a case-by-case basis after consultation between the Investigator and Sponsor with the specific reason for the exception noted.

2. Subjects with poorly controlled hypertension during Study C-935788-047 or C-935788-048, defined as persistent or repeated systolic $\geq$ 140 mmHg, or diastolic $\geq$ 90 mmHg whether or not the subject is receiving antihypertensive treatment.

3. Subjects with the following laboratory abnormalities at the time of enrollment (Day 1): a leukocyte count < 2,000/µL, an ANC of < 1,000/µL, lymphocyte count < 750/µL, Hgb < 10 g/dL, or transaminase levels (ALT, AST) > 1.5 x ULN, bilirubin > 1.5 x ULN, or estimated glomerular filtration rate (eGFR) < 30 mL/min.

4. Subjects who have a significant infection, an acute infection such as influenza, or known inflammatory process at the time of enrollment into this study.

5. Subjects who have received any blood or blood products within the 2 weeks prior to enrollment (IVIg or anti-D are allowed if used for rescue therapy).

7.0 STUDY PROCEDURES

The study procedures to be performed at each visit are shown in Table 2.

7.1 Treatment Period

7.1.1 Enrollment (Day 1)

Subjects must be willing to sign and date an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved informed consent form (ICF) prior to participating in any study-specific procedure activities. Subjects will retain their same Subject ID number as per Study C-935788-047 or C-935788-048, as applicable.

Subjects who have completed the Week 24 assessments in the previous ITP study within 7 days of enrollment in the extension study do not need to repeat these same assessments. The assessments performed during the Week 24 visit in the prior ITP study will be used to qualify subject for enrollment in the extension study. The subject must sign the ICF prior to enrollment in the extension study. The following assessments must be performed in order for a subject to be eligible for the extension study.

All local and central laboratory results must be reviewed for eligibility prior to enrollment.

- Inclusion/Exclusion Criteria
- SF-36, (must be administered prior to any other study specific procedures (refer to Appendix 5)
- Physical examination, vital signs, and KPS (refer to Error! Reference source not found.)
- Concomitant medications
- Bleeding Assessments by ITP Bleeding Scale (IBLS) (refer to Appendix 7)
- 12-lead electrocardiogram (ECG)
- Complete blood count (CBC) with differential and reticulocyte count
- Platelet count (performed at institutional or local lab)
- Serum chemistry
- Immunoglobulin levels
- Urinalysis
- Pregnancy test (for females of childbearing potential)
- AEs

Table 2: 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 (Appendix 7) and WHO (Appendix 8) 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

Baseline measurements will be the last measurement for the corresponding variable prior to the first randomized dose (Visit 3) in the C-935788-047 or C-935788-048 study.

Once a subject has been enrolled, a new bottle(s) of fostamatinib will be dispensed.

7.1.2 Treatment Visits

The treatment period begins at the time of enrollment and may continue up to a total of 60 months. Over the course of the study, subjects will be expected to visit the clinic monthly for the first 18 months, followed by every 2 months for the remainder of the study. Assessments including platelet counts will be performed to evaluate the safety and efficacy of fostamatinib, and to determine if a dose adjustment is required. All visits are determined by the date of enrollment and should occur within the windows specified (refer to Table 2 for the complete schedule of study procedures).

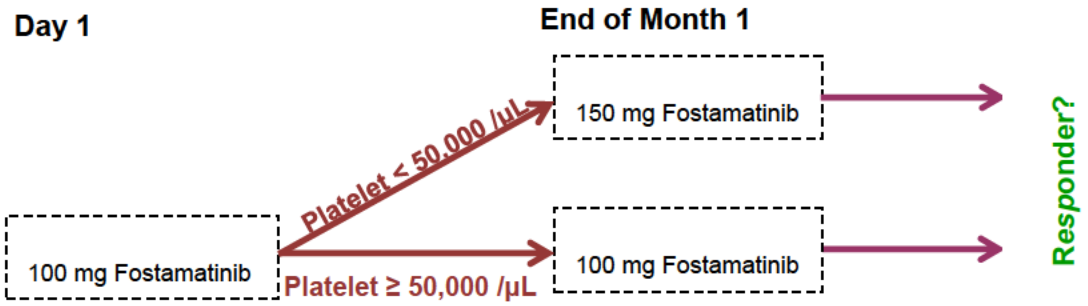
Study drug accountability will be performed at each visit. New bottle of fostamatinib will be dispensed using the IWRS at each visit. Used bottles will be returned for accountability. At the final visit of the treatment period, final study drug accountability will be performed.

7.2 Dose Adjustments

7.2.1 Dose Escalation for Subjects Not Responding at End of Month 1

The initial dose will be determined by a subject's response to treatment in Study C-935788-047 or C-935788-048 (see Section 5.3). At the end of Month 1 (approximately Day 30), subjects who initiated dosing at fostamatinib 100 mg PO *bid* in the extension study (and who have not previously had a dose reduction) should have their dose increased to fostamatinib 150 mg PO *bid* if the platelet count remains below 50,000/μL and the study drug has been well tolerated (see Figure 3). All subjects whose dose is escalated should continue to be monitored carefully for AEs associated with fostamatinib treatment.

Figure 3: Dose Escalation (Subjects starting at 100 mg *bid* who have not Previously had a Dose Reduction)



The dose may be escalated beginning at Month 1 and any visit thereafter.

7.2.2 Dose Adjustments Due to Adverse Events

Treatment with fostamatinib has been associated with AEs that may require temporary interruption of the study drug and/or a reduction in study drug dose. Modification of study drug administration may be required under the following circumstances:

- Increases in ALT, AST, or bilirubin (refer to Appendix 1 for guidance regarding LFT-related dose adjustments)
- ANC <1000/mm^3 or 1.0 x 10^9/L (refer to Appendix 2 for guidance regarding management of neutropenia)
- Severe diarrhea (refer to Appendix 3 for guidance regarding diarrhea-related dose adjustments) [(2)]
- Increase in BP to > 140/90 mmHg (refer to Appendix 4 for guidance regarding BP-related dose adjustments)
- Other severe or life-threatening AEs considered related to study drug administration

Subjects who have their dose reduced may be considered for a re-escalation of the study drug dose, following resolution of the AE resulting in dose reduction, and only after consultation with the Medical Monitor. If a subject experiences additional dose-limiting AEs, the dose of study drug may be further reduced to a dose as low as 100 mg *qd*. When dose reduction results in a once-daily dose of fostamatinib, subjects will take the daily study drug dose in the morning.

Table 3 details the strategy for dose adjustment in subjects who experience AEs requiring dose reduction.

Table 3: Dose Adjustment

Dose	Dose Level -1	Dose Level -2	Dose Level -3a	Dose Level -4a
100 mg PO bid	150 mg PO qd	100 mg PO qd	discontinue	----
150 mg PO bid	100 mg PO bid	150 mg PO qd	100 mg PO qd	discontinue

a. The Sponsor's Medical Monitor should be consulted prior to consideration of dose modification to levels -3 or -4.

7.2.3 Non-Diarrhea Gastrointestinal Toxicity

Nausea, vomiting, and abdominal pain have been reported in association with fostamatinib treatment. Symptomatic treatment, (eg, omeprazole or ranitidine for gastric distress) should be initiated promptly. In the event of significant upper abdominal pain/distress, consideration should be given to the possibility of pancreatitis and serum amylase and lipase should be monitored.

7.3 Discontinuation of Nonresponders

After 3 months (12 weeks) of treatment, (and a minimum of 4 weeks treatment at 150 mg PO *bid*, unless this higher dose was not tolerated), any subject whose platelet count consistently

remains < 50,000/µL should be discontinued from the study, unless tangible clinical benefit from the use of fostamatinib is evident and the Sponsor agrees (discuss any exceptions with the Sponsor's Medical Monitor). Examples of tangible clinical benefit may include, but are not limited to:

- Credible increase in platelet count (eg, increase in platelet count of at least 20,000/µL over the initial baseline to a count ≥ 30,000/µL)
- Reduction in bleeding
- Reduction in the need for rescue therapy

7.4 Rescue Therapy

Certain therapeutic regimens for ITP will be permitted for subjects with platelet counts < 50,000/µL who need "rescue" support of the platelet count.

Circumstances in which "rescue" therapy can be administered include:

- Platelet count < 50,000/µL and at immediate risk of bleeding or with clinically significant bleeding or wet purpura
- Platelet count < 50,000/µL and requires urgent or emergent surgery

Allowed therapeutic regimens include:

- IVIg: up to 1 g/kg x 1-3 days, or
- IV anti-D: up to 50-75 µg/kg x 1-2 days, or
- IV methylprednisolone up to 1 g/day x 1-3 days or oral dexamethasone up to 40 mg/day x 1-2 days or oral prednisone up to 1 mg/kg/day x 1-3 days

The Investigator must discuss all instances of "rescue therapy" with the Sponsor's Medical Monitor, in advance of initiating the therapy whenever possible.

7.5 Study Follow-Up

Subjects will be instructed to return to the clinic 2 weeks following the last dose of study drug for follow-up study assessments. If a SAE is present at the last visit, follow-up should occur as indicated in Section 9.3.

7.6 Definition of Study Procedures

7.6.1 Physical Exam

The initial physical exam should include evaluation of the head, eye, ear, nose, and throat, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems as well as an assessment of the Karnofsky Performance Status (Appendix 6). Physical examinations will include weight at the enrollment visit only. Subsequent examinations may be symptom-directed at the discretion of the Investigator. Physical examinations will be performed

as per the study schedule in Table 2. Any new or worsened abnormalities should be recorded as AEs after enrollment. No rectal or pelvic examination is required.

7.6.2 Karnofsky Performance Status Assessment

The KPS [(3)] is a widely used method used to assess the functional status of patients. KPS will be collected as part of the eligibility criteria. The KPS describes the patient's functional status using percentage value ranges from 100%, no evidence of disease to 0%, death. The assessor must also be the same person who is performing the physical exam for the study visit.

7.6.3 Vital Signs

Vital signs (including blood pressure, pulse, and temperature) will be assessed at each study visit. All blood pressure determinations should be made with the subject seated and taken after the subject rests for 3 minutes. If the initial blood pressure at any visit is > 130 mmHg systolic or > 80 mmHg diastolic, the blood pressure should be taken at least 2 additional times at least 5-10 minutes apart, and all 3 measurements will be recorded in the eCRF.

7.6.4 Bleeding Assessment

Bleeding symptoms will be assessed using the IBLS at each study visit. [(4)] The IBLS will include assessment of bleeding at 9 anatomical sites over the past week graded from 0 (none) to 2 (marked bleeding). Assessment of bleeding at 2 sites, skin and oral, should be assessed by physical examination (see Appendix 7).

The World Health Organization bleeding scale (Appendix 8) was collected during the first 2 years of treatment, but has been discontinued in Version 4 of the protocol.

The assessor must be a physician, doctor of osteopathic medicine, physician's assistant, or nurse practitioner. The assessor must also be the same person who is performing the physical exam for the study visit. The IBLS is to be performed by the same assessor for each subject at each study visit, whenever possible.

7.6.5 Electrocardiogram

A 12-lead ECG will be obtained after 5 minutes of rest in the supine position using equipment at the site according to the schedule in Table 2. The investigator or designee will evaluate the ECG for abnormalities.

7.6.6 Laboratory Tests

Laboratory samples will be obtained according to the schedule in Table 2. The following tests are to be collected and analyzed for the study

- Platelet Counts (performed at institutional/local lab)
- Hematology: red blood cell count (RBC); white blood cell count (WBC), hemoglobin, hematocrit, WBC differential (ANC (segmented, bands, total), lymphocytes, eosinophils

and basophils), MCHC, MCH, MCV, MPV, RDW, and reticulocyte count (performed at central lab)

- Serum chemistry: Na, K, Cl, bicarbonate (CO_2), Ca, PO4, BUN, creatinine, globulin, glucose, LDH, AST, ALT, alkaline phosphatase, total bilirubin, total protein, albumin (performed at central lab)

- Liver function tests: ALT, AST, alkaline phosphatase (ALP), lactate dehydrogenase (LDH) as well as total, direct, and indirect bilirubin (performed at central lab; if LFTs are being followed more frequently due to elevations, they may be performed at the institutional/local lab)

- Quantitative serum immunoglobulin levels: IgM, IgG, and IgA (performed at central lab)

- Urinalysis: appearance, glucose, ketones, blood, protein, nitrate, bilirubin, specific gravity, pH, urobilinogen, and leukocytes. If positive for blood or protein trace, then include microscopy (performed at central lab)

All subjects' laboratory results with clinically significant abnormal values should be followed regularly until the values return to the normal range or until a more plausible alternative cause, other than drug-related AE, is identified.

7.6.7 Pregnancy Tests

Urine pregnancy tests (performed at the site) will be obtained at intervals throughout the study. Subjects who have a confirmed positive pregnancy test at any time during the study will be discontinued from further study drug administration and will be followed for safety (see Section 9.4).

7.6.8 Short Form 36 (SF-36) Questionnaire

Subjects will complete the SF-36 v2, standard version, a generic health survey consisting of 36 questions, (Appendix 5), yielding 8 health-related quality of life (HRQoL) domains (physical functioning, role-physical, bodily pain, general health, vitality, social function, role-emotional, mental health) as well as a psychometrically based physical component score (PCS) and mental component score (MCS). The SF-36 will be administered according to the schedule in Table 2. At visits where the SF-36 is administered the SF-36 should be the first assessment performed. Subjects must complete the questionnaire on their own without input of study personnel.

7.7 Concomitant Therapies

Concomitant therapies will be recorded in the eCRF at all visits.

7.7.1 Allowed ITP Therapies

Subjects may continue concurrent therapies for ITP that were allowed at entry (ie, glucocorticoids at a dose less than the equivalent of 20 mg prednisone daily, or azathioprine, or danazol). Consideration can be given to tapering the dose of any concomitant ITP medication, in

subjects whose platelet count is stable at ≥ 50,000/μL. New treatments for ITP may not be added.

7.7.2 Restricted Medications Unrelated to ITP

Due to the potential for drug-drug interactions with fostamatinib, the following specific treatments are either not allowed or restricted during the course of this study, (see Table 4 and the additional information included in Appendix 9).

Table 4: Restricted Medications

Drug	Restriction
CYP3A4 inhibitors and inducers	The active metabolite of fostamatinib is metabolized by CYP3A4. Restrictions on the co-administration of CYP3A4 inhibitors and inducers are described in Appendix 9.
P-gp substrate	Fostamatinib is an in vitro inhibitor of P-gp. Restrictions on the co-administration of P-gp substrates (eg, digoxin) are described in Appendix 9.
HMG-CoA reductase inhibitors	Fostamatinib may increase plasma concentrations of HMG-CoA reductase inhibitors. Information on the co-administration of HMG-CoA reductase inhibitors is found in Appendix 9.

7.8 Pharmacokinetic Samples

At Month 2, blood samples for PK analysis will be collected from a subset of 12 subjects at selected sites. Subjects participating in the PK portion of the study will be instructed not to take the morning dose of fostamatinib on the day of Month 2 visit. Subjects will remain at the clinic for up to 9 hours during the visit. When a subject arrives at the clinic, the time of the last dose of fostamatinib will be recorded in the eCRF.

Samples (4 mL) of whole blood to provide a minimum of 2 mL plasma for PK analysis, will be collected into the appropriately labeled tubes containing K_2EDTA anticoagulant at the following time points:

- pre-dose and 0.5, 1, 2, 4, 6, and 8 hours postdose

The time each PK sample is drawn as well as the time the morning dose is taken (at the clinic) will be recorded in the eCRF.

Samples will be shipped to and stored at the central laboratory at -70°C during the course of the study. Samples will then be transferred to and analyzed at the corresponding bioanalytical laboratory.

After completion of the study, samples may be stored for an additional 5 years for future metabolite identification and/or further evaluation of the bio-analytical method. This data will be used for internal exploratory purposes and will not be included in the clinical report. All samples will be destroyed after analysis or expiration of the 5 year time period.

The following PK parameters will be estimated for R406:

- C_{max}
- T_{max}
- AUC_{0-8}

C_{max} and T_{max} will be taken directly from the data; AUC_{0-8} will be calculated using the linear trapezoidal method. Descriptive measures of plasma levels will be provided for each time point and will include the geometric mean and associated 95% CI.

Actual blood sampling times will be used for all PK analyses. Nominal blood sampling times will be used for summary statistics of plasma concentrations and graphs of mean plasma concentrations versus time.

7.9 Withdrawal from Study

Subjects will be discontinued from study treatment in the following situations:

- Subject decision. A subject is free to withdraw consent and discontinue participation in the study at any time.
- AE based on Investigator judgment
- Subject is uncooperative or noncompliant and will not/cannot adhere to study responsibilities, including failure to complete patient diary or appear for study visits
- Subject was erroneously enrolled in the study
- Pregnancy in a female participant
- Subject lost to follow-up despite the diligent efforts of site personnel to trace subject

Subjects may be withdrawn from study treatment and from the study in the event of lack of platelet response (defined as platelet count < 50,000/μL) following 3 months (12 weeks) of treatment unless Sponsor approval is obtained.

Subjects who are withdrawn from the study during the treatment period will have a withdrawal visit equivalent to the Follow-up Visit assessments. The reason for withdrawal must be noted on the eCRF. If an SAE is present at the withdrawal visit or at the subject's last participation in the study, the SAE should be followed as described in Section 9.2.

7.10 Study Completion and Early Termination

The study will end upon completion of all protocol procedures. Rigel may terminate the study at any time. Conditions that may warrant early termination of the study include, but are not limited to, discovery of an unacceptable risk to subjects enrolled in the study or the decision by Rigel to suspend or discontinue development of the study drug for this indication. If the Investigator

becomes aware of any circumstances during the study that may reasonably indicate that the study should be terminated, the Investigator will immediately notify Rigel and will cooperate with Rigel in the investigation and evaluation of such circumstances and any decision of Rigel that may follow.

Conditions that may warrant termination of the study at a site include, but are not limited to:

- Failure of the Investigator to comply with pertinent laws or regulations
- Submission of false data or material information by the investigational site to Rigel
- Failure by the investigational site to adhere to protocol requirements

8.0 STUDY DRUG

8.1 Study Drug Description

Fostamatinib is supplied as orange film coated tablets in two dosage strengths: 100 mg and 150 mg.

Study drug will be labeled in accordance with Good Manufacturing Practices (GMP), local regulatory requirements, and all other applicable laws.

8.1.1 100 mg Tablets

Fostamatinib 100 mg tablets are supplied as orange film coated, plain, round, biconvex tablets with a diameter of 9 mm. Each tablet has a total weight of 346 mg and contains 100 mg of fostamatinib and the following inert excipients: mannitol, sodium hydrogen carbonate, sodium starch glycolate, povidone, magnesium stearate, hypromellose, titanium dioxide, macrogol 400, ferric oxide (yellow) and ferric oxide (red).

8.1.2 150 mg Tablets

Fostamatinib 150 mg tablets are supplied as orange film coated, plain, oval, biconvex tablets measuring 7.25 mm x 14.5 mm. Each tablet has a total weight of 520 mg and contains 150 mg of fostamatinib and the following inert excipients: mannitol, sodium hydrogen carbonate, sodium starch glycolate, povidone, magnesium stearate, hypromellose, titanium dioxide, macrogol 400, ferric oxide (yellow) and ferric oxide (red).

8.2 Storage

Supplies of fostamatinib tablets will be stored at the study site in a secure location with restricted access and room temperature (below 30° C) with temperature monitoring.

8.3 How Supplied/Study Drug Dispensation

Fostamatinib tablets are packaged in bottles. Each bottle will contain 70 tablets to provide a 30-day supply of study drug plus overage for an additional 5 days of dosing, if needed. At Enrollment (Day 1) a single bottle of fostamatinib will be dispensed.

Subjects should be instructed to bring the bottle containing unused study drug back to the clinic at the next visit. At each monthly visit, following accountability, 1 new bottle of study drug will be dispensed to cover dosing until the next visit.

The procedure outlined above for accountability and dispensing of fostamatinib should be followed for all subsequent visits.

8.4 Study Drug Administration

Fostamatinib will be self-administered, *bid* by mouth, once in the morning and once in the evening for 24 months. In the event that the dose of fostamatinib is reduced to once daily due to AEs, study drug will be taken in the morning.

If a subject misses a scheduled dose, they should be instructed to continue to take their next dose as normal and should not take 2 doses at the same time.

Fostamatinib may be taken with or without food. Subjects should be instructed not to take fostamatinib with grapefruit juice or any other food or drink known to inhibit CYP3A4. Subjects who experience gastric upset following dosing, may be advised to take fostamatinib with food.

8.5 Study Drug Accountability/Drug Compliance

The Investigator will be responsible for monitoring the receipt, storage, dispensation, and accountability of all study drug according to accepted medical and pharmaceutical practice. All documentation of study drug shipments must be retained by the site. Accurate, original site records must be maintained of study drug inventory and dispensation. All records must be made available to the Sponsor (or designee) and appropriate regulatory agencies upon request.

9.0 ADVERSE EVENTS

9.1 Definitions

Adverse Event (AE): An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug.

For the purposes of this clinical study, AEs include only treatment emergent events which are either new or represent detectable exacerbations of pre-existing conditions. [5, 6]

AEs may include, but are not limited to:

- Subjective or objective symptoms spontaneously offered by the subject and/or identified by the Investigator or study staff including laboratory abnormalities of clinical significance
- Any AEs experienced by the subject through the completion of final study procedures
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the target disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as venipuncture)

The following are NOT considered an AE:

- **Pre-Existing Condition:** A pre-existing condition is not considered an AE unless the severity, frequency, or character of the event worsens during the study period. For the purpose of this study, pre-existing conditions are those documented in the Study C-935788-047 or C-935788-048 as medical history.
- **Pre-Planned Hospitalization:** A hospitalization planned prior to signing the ICF is not considered an SAE but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration but not performed prior to enrollment in the study will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Hospitalizations for social reasons or due to long travel distances are also not considered SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

Serious Adverse Event:

Note: The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition.

An SAE or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. (With regards to determining if an AE is serious, "life-threatening" is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the Investigator or the Sponsor believes that an AE meets the definition of life threatening, it will be considered life-threatening.)
- Requires in-patient hospitalization or prolongation of an existing hospitalization
- Results in persistent or significant disability/incapacity (eg, the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect

Medical and scientific judgment should be exercised in deciding whether other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse). Given that the Investigator's perspective may be informed by having actually observed the event and Rigel is likely to have broader knowledge of the study drug and its effects to inform its evaluation of the significance of the event, if either Rigel or the Investigator believes that the event is serious, the event will be considered serious.

Suspected Adverse Reaction:

Any AE for which there is a "reasonable possibility" that the study drug caused the AE will be regarded as a Suspected Adverse Reaction by Rigel.

"Reasonable Possibility," for the purposes of safety reporting, means there is evidence to suggest a causal relationship between the study drug and the AE. Examples of types of evidence that would suggest a causal relationship between the study drug and the AE are:

- A single occurrence of an event that is uncommon and known to be strongly associated with study drug exposure (eg, angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens-Johnson syndrome).
- One or more occurrences of an event that is not commonly associated with study drug exposure but is otherwise uncommon in the population exposed to the study drug (eg, include tendon rupture or heart valve lesions in young adults or intussusception in healthy infants). If the event occurs in association with other factors strongly suggesting causation (eg, strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive; but often, more than one occurrence (from one or multiple studies) would be needed before the Sponsor could make a determination of whether the study drug caused the event.

- An aggregate analysis of specific events that can be anticipated to occur in the study population independent of study drug exposure. Such events include known consequences of the underlying disease or condition under investigation (eg, symptoms, disease progression) or events unlikely to be related to the underlying disease or condition under investigation but commonly occur in the study population independent of drug therapy (eg, cardiovascular events in an elderly population). An aggregate analysis (across studies) will identify those events that occur more frequently in the study drug treatment group than in a concurrent or historical control group.

This definition of *suspected adverse reaction* and the application of the *reasonable possibility* causality standard is considered to be consistent with the concepts and discussion about causality in the International Conference on Harmonisation (ICH) E2A guidance.

Unexpected: An AE that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be "unexpected" (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be "unexpected" (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the study drug but are not specifically mentioned as occurring with the study drug under investigation.

Causality: The Investigator is to assess the causal relation (eg, whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

- **Probable**: A reaction that follows a reasonable temporal sequence from administration of the investigational study drug or its class of drugs; that follows a known or expected response pattern to the suspected investigational study drug; and that could not be reasonably explained by the known characteristics of that subject's clinical state or the background rate for the event in the population being studied.
- **Possible**: A reaction that follows a reasonable temporal sequence from administration; that follows a known or expected response pattern to the suspected investigational study drug; but that could readily have been produced by a number of other factors.
- **Unlikely**: A reaction that does not follow a reasonable temporal sequence from administration, or there is a reasonably compelling alternative explanation. However, causation by the investigational study drug cannot be ruled out.

Assessment of Severity: The following grading system should be used to assess severity of AEs other than diarrhea (See Appendix 3 for grading system to be used for diarrhea):

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities.
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject and which may interfere with daily activities but are usually ameliorated by simple therapeutic measures.

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment.

9.2 Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

The Investigator is responsible for ensuring that all AEs (including SAEs) that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported on the SAE page of the eCRF.

9.2.1 Adverse Event Reporting Period

The AE reporting period begins from the last dose of study drug in Study C-935788-047 or C-935788-048 and ends with the final study (Follow-Up) visit in the Study C-935788-049. All ongoing AEs from Study C-935788-047 or C-935788-048 will be followed as AEs in Study C-935788-049.

If an SAE is present at the Follow-Up Visit, it should be followed to resolution or stabilization unless the subject is lost to follow-up. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

In case of ongoing SAEs at the moment of database closure, the data obtained at the moment of database closure will be used in the statistical analysis. The follow-up of the SAE will be documented in the source documents and will be described in the final report or as an addendum as appropriate.

9.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs, whether volunteered by the subject, discovered by study staff during questioning, or detected through PE, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on an SAE form.

Each recorded AE or SAE will be described by its duration (eg, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the investigational product (see guidance above), and any actions taken.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Rigel, or designee, as described below.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

9.2.3 Expedited Reporting Requirements for Serious Adverse Events

An Investigator should report a SAE within 24 hours of his/her awareness of the event by completing and sending the provided SAE form to Rigel's authorized safety representative. Additionally, all fatal or life-threatening SAEs should be telephoned to Rigel as soon as the Investigator learns of the event.

The SAE form should be sent to the following email or fax:

Email: clinsafety@rigel.com
Fax: Refer to the Study Reference Manual

The site may contact the Medical Monitor (listed below) with questions regarding the reporting of SAEs.

Sites should contact:

9.3 Reporting of Serious Adverse Events by Sponsor

Regulatory Authorities, IRBs/IECs, and Principal Investigators will be notified of SAEs in accordance with applicable requirements (eg, GCPs, ICH guidelines, national regulations, and local requirements). The country-specific requirements, timelines, and processes for complying with these requirements are described in detail in the Study Operations Manual and/or Safety Plan.

Rigel's Safety Surveillance Committee will review and evaluate accumulating safety data from the entire clinical trial database for the study drug at appropriate intervals (eg, quarterly) to identify new safety signals or increased frequency of events. This will include an aggregate review and comparison to the control group of SAEs that were deemed as "not suspected" as being associated with use of the study drug.

9.4 Pregnancy

Although pregnancy itself is not regarded as an AE, the outcome of any pregnancy that occurs during the study must be documented.

Prior to study enrollment, females of childbearing potential must agree in the ICF to take appropriate measures to avoid pregnancy at all times during the study, commencing from the time of consent to 30 days after the last dose of study drug, and, if pregnancy occurs, they must agree to report the pregnancy and cooperate with the Investigator as set forth below.

Should a pregnancy occur, the female study participant must immediately inform the Investigator and must immediately discontinue study drug. The Investigator should counsel the study participant on any risks of continuing the pregnancy and any possible effects on the fetus in view of the subject's participation in the study. The study participant must agree to follow-up by the Investigator regarding the outcome of any pregnancy that occurs during the study. Outcome is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed by the Investigator until it is 30 days old. Any congenital anomaly/birth defect noted in the infant must be reported as an SAE.

The Investigator will notify Rigel or its authorized representative of a pregnancy occurring in a female study participant within 14 days of first becoming aware of such pregnancy using the pregnancy notification form. All follow-up information gathered by the Investigator shall be reported to the Sponsor within 14 days of Investigator's first knowledge of such information using the pregnancy exposure form.

10.0 STATISTICAL METHODS

10.1 General Considerations

Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized using frequencies and percentages.

The statistical analysis of the data obtained from this study will be performed using SAS® version 9.1 or higher. All 1-sided tests will be performed at the 0.025 significance level, and all 2-sided tests will be performed at the 0.05 significance level, unless otherwise indicated.

A full statistical analysis plan will be finalized before database lock.

10.2 Analysis Populations

The Treated population will include all enrolled and treated subjects. All efficacy endpoints will be analyzed based on the Treated population, and subjects will be analyzed according to their actual treatment. The efficacy analyses based on the Treated population will be considered the primary efficacy analyses. All analyses of safety will also be performed on the Treated Population.

The Per-Protocol (PP) population will include all subjects in the Treated population who had no major protocol violations in either study. Major protocol violations will include:

- Not receiving any study treatment
- Not receiving the correct study treatment
- Failing to meet eligibility criteria
- Other major protocol violations, as determined by a review of the data prior to database lock

All efficacy endpoints will also be analyzed based on the PP population, and subjects will be analyzed according to their actual treatment. The analyses based on the PP population will be considered secondary analyses of efficacy.

10.3 Definition of Baseline Measurements

Baseline measurements will be the last measurement for the corresponding variable prior to the first randomized dose at Visit 3 in the Study C-935788-047 or C-935788-048.

10.4 Analysis of Efficacy Endpoints

10.4.1 Primary Efficacy Endpoint

10.4.1.1 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 count defined as follows:

1) Achievement of a platelet count of at least 50,000/μL within 12 weeks of beginning active treatment
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 subject first received active treatment. Subjects 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. This endpoint will be summarized using counts and percentages, together with a 95% exact (Clopper-Pearson) CI for the true percentage.

10.4.1.2 Version 2

The second version of the primary efficacy endpoint is for the purpose of a within-subject, between-study comparison of fostamatinib and placebo among subjects 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 count, 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).

Subjects who discontinue treatment due to lack of efficacy or to an AE prior to 12 weeks following achievement of a platelet count of at least 50,000/μL, will be considered failures. The null and alternative hypotheses for the comparison of fostamatinib vs. placebo are as follows:

$$H_0: p_F = p_P \quad \text{vs.} \quad H_1: p_F \neq p_P$$

where p_F and p_P denote the true proportions achieving and maintaining a stable platelet count for fostamatinib and placebo, respectively. The null hypothesis will be tested using a 2-sided

McNemar's test conducted with a significance level of 0.05. This analysis will be performed for the Treated and Per Protocol populations.

10.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

- Duration of stable platelet response
- Proportion of subjects in whom a reduction in the dose of concomitant ITP therapy can be achieved while maintaining an adequate platelet count

Duration of stable platelet response is defined as the time, following active treatment, from when the subject 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. Subjects who drop out of the study before achieving a stable platelet response will be assigned a value of 0 for this endpoint. Subjects who drop out of or complete the study while still maintaining a stable platelet response will be censored as of the time of the last platelet measurement prior to dropping out or completing the study. For subjects who have achieved and are maintaining a stable platelet response but who discontinue treatment due to lack of efficacy or to an AE, duration of stable platelet response will be defined as the time from first achieving a platelet count of at least 50,000/μL until discontinuation of treatment. The duration of stable platelet response will be analyzed using the Kaplan-Meier method, and the Kaplan-Meier estimate of the median duration of stable platelet response will be presented together with the 95% CI for the true median.

Achieving a reduction in the dose of concomitant ITP therapy while maintaining an adequate platelet count will be summarized using counts and percentages and a 95% exact (Clopper-Pearson) CI for the true percentage. A two-sided, McNemar's test will be performed to compare the proportions of successes between the fostamatinib and placebo treatments.

10.5 Safety Endpoints

The safety outcomes of this study include the frequency and severity of bleeding according to the IBLS, the change from baseline in blood pressure, liver function, and ANC, the incidence of GI complaints, and the incidence of AEs.

The mean of the IBLS scores across visits during the treatment period will be summarized using descriptive statistics.

Descriptive statistics will be presented by visit for the actual values and the changes from baseline for systolic and diastolic blood pressure, each liver function test [ALT, AST, alkaline phosphatase, and bilirubin (total, direct, and indirect)], and ANC. The one-sample t-test will be used to test whether the mean change from baseline equals 0 for each post-baseline time point. The numbers and percentages of patients with GI complaints at any time during the treatment period will be presented for the Safety Population.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with at least one AE, at least one SAE, and at least one treatment-related AE 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. AEs will be summarized at the subject level by MedDRA system organ class (SOC) and preferred term using frequencies and percentages. AEs will also be tabulated at the event level by severity and by relationship to study treatment.

10.6 Analysis of Pharmacokinetic Endpoints

Plasma concentrations of R406 will be collected for a subset of patients at Month 2 Plasma concentrations will be summarized by time point using descriptive statistics including: the number of patients, arithmetic mean, standard deviation, geometric mean and associated 95% CI, median, minimum, maximum, and coefficient of variation for each treatment group. Nominal blood sampling times will be used for these analyses. A graph of mean plasma concentration of R406 versus nominal blood sampling time will be produced for each treatment group.

The following PK parameters will be estimated for R406: maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), and area under the plasma concentration-time curve through 8 hours ($AUC_{(0-8)}$). C_{max} and T_{max} will be taken directly from the data; $AUC_{(0-8)}$ will be calculated using the linear trapezoidal method. These PK parameters will be summarized by treatment group using descriptive statistics. Actual blood sampling times will be used for these analyses.

10.7 Determination of Sample Size

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

10.8 Handling of Dropouts and Missing Data

No imputation will be performed for missing data.

11.0 ETHICAL AND LEGAL ISSUES

This protocol was designed and will be conducted, recorded, and reported in compliance with applicable laws, rules, and regulations, including GCP. The Investigator and study staff are responsible for conducting this study in accordance with United States Code of Federal Regulations (CFR), GCP, and the Declaration of Helsinki, as well as all applicable national and international laws and regulations.

11.1 Confidentiality of Subject Personal Information

Information on the confidential treatment of subject personal information collected in the study must be provided to each subject in the Informed Consent (see Section 11.5). In addition, an authorization for the collection, use, disclosure, and transfer of subject personal information (an "Authorization"), in compliance with the applicable laws, rules, and regulations of the jurisdiction where the study is to be conducted, must be provided to each subject, either as part of the ICF or as a separate signed document (for example, in the US, a Health Insurance Portability and Accountability Act [HIPAA] Authorization will be used).

The Investigator will assign a unique identifier or code to each subject to be used in lieu of the subject's name in study documentation and in reporting of AEs for the purpose of ensuring the confidential treatment of the study participant's personal and health information. The Investigator will maintain in a secure location a master key to the subject identifier list consisting of the unique subject identifiers, subject names, and dates of birth to allow unambiguous identification of each subject included in the study.

Researchers, monitors, and auditors shall be required to strictly adhere to professional standards and applicable law concerning the confidential treatment of the subject information.

11.2 Institutional Review Board/Independent Ethics Committee

The protocol, ICF, any advertisements to recruit subjects, or materials to be given to the subjects during the study must be approved by an appropriate IRB/IEC. IRB/IEC approval must also be obtained for any protocol amendments and ICF revisions before implementing the changes.

The Investigator is responsible for providing the IRB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/IEC must comply with current US regulations (§ 21 CFR 56), as well as national and international regulations.

Rigel will not initiate the first study drug shipment to the study site until the study site provides Rigel or its authorized representative with:

- A copy of the IRB/IEC (and Regulatory Authority, where applicable) letter that grants formal approval; and
- A copy of the IRB/IEC-approved ICF (and Regulatory Authority-approved ICF, where applicable).

11.3 Changes to the Study

Before any significant changes to the design of the study are made, a protocol amendment will be issued by Rigel that must be submitted to and approved by the IRB/IEC and signed by the Investigator. No other change in the study procedures, except to protect the health, safety, or welfare of subjects in the study, is permitted or shall be effected without the mutual agreement of the Investigator and Rigel.

11.4 Protocol Deviations, Violations, Waivers and Exemptions

A protocol deviation is defined as "a variation from processes or procedures defined in a protocol." Deviations usually do not preclude the overall evaluability of subject data.

However, if a protocol violation (defined as "a significant departure from the processes and procedures that were required by the protocol") occurs, it may result in data that are not deemed evaluable for a protocol analysis and/or may require subject(s) to be discontinued.

If a protocol violation has occurred, a protocol waiver must be approved by the Medical Monitor in order to allow the subject to continue in the study.

A protocol exemption is defined as:

- An allowance to enroll a specific subject into the study who has a conflict with a specific inclusion or exclusion criterion; or
- An allowance to continue subject participation in a study when a departure from the study protocol is planned or expected.

A protocol exemption must be approved by the Medical Monitor in advance of the protocol departure taking place.

11.5 Informed Consent

The ICF and process for obtaining informed consent must comply with the US regulations (§ 21 CFR Part 50), as well as other applicable national and international laws, rules, and regulations. The ICF will document the study-specific information the Investigator or his/her designee provides to the subject and the subject's agreement to participate in the study and to comply with the instructions of the Investigator and study staff. The Investigator/designee will fully explain in terms understandable to the subject the nature of the study, along with the aims, methods, anticipated benefits, potential risks, and any discomfort that participation in the study may entail. The ICF must be signed and dated by the subject before the subject participates in any study-related activities. The original and any amended signed and dated ICFs must be retained in the subject's file at the study site, and a copy must be given to the subject at the time that it is signed by the subject. The Investigator must also maintain a log of all informed consents obtained.

The Investigator/study staff must provide Rigel or its authorized representative with the proposed ICF for Rigel's review and comment prior to submitting the ICF to the IRB/IEC. The study

center and the Investigator will include Rigel's proposed changes to the ICF prior to submitting the ICF to the IRB/IEC for review and approval.

11.6 Liability, Insurance, and Financing

If, during the study, a subject experiences an illness or potential study drug or study procedure side effect or other possible study-related injury, appropriate medical care will be provided by the Investigator/designee.

Rigel Pharmaceuticals, Inc., the sponsor of the study, will provide reimbursement to the site for the cost of any medical treatment of any injury or illness caused by the study drug or the protocol procedures, except to the extent that any such injury or illness was caused by the negligence of the Investigator or study personnel, for example, their failure to follow the protocol, or the subject's failure to follow the Investigator's instructions.

The ICF will include a description of this reimbursement policy, in addition to any provisions required by applicable national or international regulations. Financial compensation for lost wages, disability, or discomfort due to the study drug or protocol procedures is not offered by the Sponsor.

The Sponsor is insured against potential liabilities caused by the study drug and/or protocol procedures. A confirmation or certificate of such insurance and essential information about insurance coverage will be provided by the Sponsor upon request.

A separate written contract covering the obligations of the Sponsor and of the Institution and Investigator with regards to the study is required before the study drug may be delivered to the study site.

For all Rigel clinical studies, each Investigator and Subinvestigator (as designated on the Form FDA 1572) will provide a signed Financial Disclosure Form in accordance with § 21 CFR 54. Each Investigator will notify Rigel or its authorized representative of any relevant changes to the information included on such Financial Disclosure Form during the conduct of the study and for 1 year after the study has been completed.

12.0 DATA COLLECTION, RETENTION, AND MONITORING

12.1 Source Data

The Investigator/study staff must maintain adequate and accurate source documentation to document the treatment and study course of a subject and to substantiate the integrity of the trial data submitted for review to the regulatory authorities. These documents include investigators' study files and original subject clinical source documents generated at the study site. The term "original" means the first recording of the data.

The Investigator will ensure the study files are maintained, including the eCRFs and query forms, protocol/amendments, IRB/EC and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Subject source documents may include, but are not limited to, subject hospital/clinic records, hospital and/or clinic or office records documenting subject visits, ICFs, subject questionnaires, laboratory reports, ECGs, and treatments or procedures pertaining to SAEs. The investigator must assure that all original source documents are available to support monitoring activities.

12.2 Electronic Case Report Forms

Electronic Case Report Forms (eCRFs) will be used to collect the clinical study data. The eCRFs will be entered by study staff and must be completed for each screened subject with all required study data accurately recorded.

The eCRF exists within an EDC system with controlled access managed by Rigel or its authorized representatives for this study. Study staff will be appropriately trained in the use of eCRFs and application of electronic signatures before the start of the study and prior to being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The Investigator will attest that the information contained in the eCRFs is true by providing electronic signature within the EDC system prior to database lock. After database lock, the Investigator will receive a copy of the subject data (eg, CD-ROM, or other appropriate media) for archiving at the study site.

At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data.

12.3 Monitoring

This study will be monitored by Rigel or its authorized representative in accordance with current GCP. The study monitor(s) are responsible for monitoring whether the study is conducted according to applicable Rigel or its authorized representative standard operating procedures (SOPs), the protocol, and other written instructions and regulatory guidelines. Training will be provided for key investigative personnel in all aspects of study conduct.

In order to assure the data are accurate, complete, and verifiable, and that the conduct of the study is in compliance with the currently approved protocol, ICH, GCP, and with the applicable regulatory requirements, it is mandatory that the Rigel or its authorized representative, the FDA, and other regulatory have access to all original electronic and paper source documents (as described in Section 12.1 and Section 12.2) at reasonable times and upon reasonable notice. During the review of source documents, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations (refer to Section 11.1).

Monitoring visits will occur as required during the conduct of the study. The study monitor will physically visit the study site(s) at least 2 times during the study duration (interim and close out visits) or more if deemed necessary and will be allowed, on request, to inspect the various records of the study. The study monitor will contact the study site via telephone and written communication regularly throughout the conduct of the study to maintain current and personal knowledge of the study. It will be the study monitor's responsibility to remotely inspect the eCRFs at regular intervals throughout the study to verify the adherence to the protocol and the completeness, correctness, and accuracy of all eCRF entries. The study monitor should have access to laboratory test results and any other source records and data needed to verify the entries on the eCRFs. The Investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Upon completion or termination of the study, the Investigator will notify the IRB/EC with a final report and provide Rigel or authorized representatives with a copy of the final report.

12.4 Data Quality Assurance

The handling of data, including data quality assurance, will comply with this protocol, the informed consent, the contract between the site and Rigel, and all applicable regulatory requirements and guidelines (eg, ICH and GCP) and Rigel's authorized representative's SOPs and working instructions. Data management and control processes and quality assurance specific to this study will be described in a data management/validation plan. All steps and actions taken regarding data management and quality assurance will be documented in a data handling report.

12.5 Data Collected by Contractors

Rigel will be responsible for ensuring that the collection, evaluation, and archiving of study data by Rigel's representatives and vendors adheres to the protocol specifications and GCP requirements.

12.6 Availability and Retention of Investigational Records

A file for each subject must be maintained that includes the signed ICF (including confidential treatment of subject information) and copies of source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived and will comply immediately with any reasonable request of Rigel or its authorized representative to confirm information recorded on eCRFs.

Subject identity information will be maintained by the Investigator for 15 years. All other essential documentation will be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. Should the Investigator/ Institution be unable to continue maintenance of subject files for the full 15 years, Rigel will assist in this regard. Rigel will inform the Investigator/Institutions as to when these documents no longer need to be retained.

Essential documentation includes, but is not limited to, the Investigator's Brochure; signed protocol and amendments; signed Form FDA 1572 (or equivalent), signed Informed Consent and HIPAA Authorization (US only); signed (electronically), dated, and completed eCRFs, and documentation of eCRF corrections; source documents; notification of SAEs and related reports; any study drug dispensing and accountability logs; shipping records of investigational product and study-related materials; dated and documented IRB/IEC approval; normal laboratory values; decoding procedures for blinded studies; curricula vitae for study staff; and pertinent study-related correspondence. No study document or image (eg, scan, radiograph, ECG tracing) should be destroyed without prior written agreement between Rigel and the Investigator. Should an Investigator wish to move the study records to another location, advance written notice will be given to Rigel. Study records will not be transferred to another party without Rigel's advance written consent.

Rigel or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time prior to, during, or after completion of the clinical study. In the event of such an inspection, Rigel will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

The Investigator agrees that all data and information that is generated as a result of conducting the study or that is received from Rigel or its authorized representative, including this protocol, eCRFs, and any other study information, is and shall remain the sole and exclusive property of Rigel. The Investigator and study staff will not disclose any Rigel information to any third party (except employees or agents of the study site directly involved in the conduct of the study who need to know the information for the purpose of carrying out the study and who are contractually bound to maintain its confidentiality) without prior written consent of Rigel. The Investigator further agrees to take all reasonable precautions to prevent the disclosure of Rigel confidential information by any employee or agent of the study site to any third party or otherwise into the public domain.

13.0 SUPERVISION OF THE STUDY

The Investigator is responsible for the supervision of study conduct in accordance with the protocol, including collection of and maintenance of adequate and appropriate study documentation. The Investigator may delegate some of the work involved in the conduct of the study. The Investigator shall ensure that all study staff are qualified by education, experience, and training to perform their specific responsibilities in relation to the study. All individuals involved in the conduct of the study and working with the study documentation must complete the Delegation of Authority Log.

14.0 DISCLOSURE/PUBLICATION OF DATA

All results derived from the study are the exclusive property of Rigel Pharmaceuticals, Inc. and are considered confidential to Rigel. Written permission from Rigel is required prior to disclosing any information relative to this study or the study drug.

After conclusion of the study, Investigators in this study may communicate, orally present, or publish in scientific journals or other scholarly media the results of the study from their study site ***only after the following conditions have been met:***

- The results of the study in their entirety have been publicly disclosed by or with the consent of Rigel in an abstract, manuscript, or presentation form; or
- The study has been completed at all study sites for at least 2 years; or
- As otherwise permitted in writing and in advance by Rigel.

The Investigator will submit to Rigel any proposed publication or presentation along with the name of the respective scientific journal or presentation forum at least 30 days prior to submission of the publication or presentation. The Investigator will comply with Rigel's request to delete references to its confidential information in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection on the contents of any publication if deemed necessary by Rigel. This requirement should not be construed as a means of restricting publication but is intended solely to assure concurrence regarding data, evaluations, and conclusions and to provide an opportunity to share with the Investigator any new and/or unpublished information of which he/she may be unaware.

15.0 REFERENCES

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4. Page LK, Psaila B, Provan D, et al. The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. Bri J Haem 2007; 138(2): 245–248. Epub 2007/06/05.

5. FDA. Guidance for Industry and Investigators: Safety reporting requirements for INDs and BA/BE studies. Food and Drug Administration (FDA); 2012.

6. ICH. Guideline for industry: clinical safety data management: definitions and standards for expedited reporting (ICH-E2A). International Conference on Harmonisation (ICH) 1995.

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8. Maitland ML, Bakris GL, Black HR, et al. Initial assessment, surveillance, and management of blood pressure in patients receiving vascular endothelial growth factor signaling pathway inhibitors. J Nat Canc Instit 2010; 102(9): 596–604.

9. FDA. Guidance for Industry: Drug-induced liver injury: premarketing clinical evaluation. In: FDA,CDER,CBER.http://www.fda.gov/downloads/drugs/guidancecompliance regulatory information/guidances/ucm174090.pdf: issued July 2009.

10. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47(1): 207–214.

Appendix 1: Dose Modification for Possible Drug-Induced Liver Injury

The Investigator is responsible for determining whether the subject meets Hy's law criteria for severe liver injury; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN) plus total bilirubin (TBL) > 2x ULN and alkaline phosphatase (ALP) < 2x ULN.

- **Note**: Fostamatinib is an inhibitor of UGT1A1, the enzyme responsible for the glucuronidation of bilirubin; occasionally an isolated increase in total and **unconjugated (**indirect) bilirubin may be observed. Study drug should not be interrupted for an isolated increase in total and unconjugated (indirect) bilirubin.

- The study Medical Monitor should be notified immediately of any potential case meeting Hy's law criteria.

Dose Adjustment

Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3[a]	Dose Level -4[a]
100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue	----
150 mg PO *bid*	100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue

a The Sponsor's Medical Monitor should be consulted prior to consideration of dose modification to levels -3 or -4.

Identification

If AST or ALT ≥ 3x ULN and **total** bilirubin > 2x ULN, with ALP < 2x ULN (Hy's law criteria met), please follow the instructions below:

- Stop study drug treatment and **contact the Sponsor's medical monitor immediately to discuss the data and consider withdrawal of** the subject from the study for possible drug-induced liver injury.

- The Investigator will follow the subject until liver biochemistry parameters and any appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.

- The Investigator will investigate the etiology of the event and perform diagnostic investigations as discussed with the Sponsor's Medical Monitor.

If AST or ALT ≥ 3x ULN **or** TBL > 2x ULN, and the subject is exhibiting the following symptoms: nausea, vomiting, abdominal pain:

- Study drug administration should immediately be interrupted.
- LFTs, including bilirubin and alkaline phosphatase should be repeated every 3 days/72 hours until ALT/AST or TBL returns to < 1.5x ULN.
- When the ALT/AST or TBL returns to < 1.5x ULN study drug may be restarted at dose level -1.

If AST or ALT ≥ 3x ULN **or** TBL > 2x ULN and subject is asymptomatic:

- Repeat LFTs, including bilirubin and ALP, within 72 hours.
- If repeat testing shows an increase in ALT/AST or TBL and the ALT/AST value exceeds 5x ULN, interrupt study drug administration.
- LFTs, including bilirubin and alkaline phosphatase should be repeated every 3 days/72 hours until ALT/AST is decreasing, and should be followed until transaminase returns to < 1.5x ULN.
- Upon return of ALT/AST or TBL to < 1.5x ULN, study drug may be restarted at dose level -1.

Source: FDA 2009 [9]

Appendix 2: Management of Neutropenia

Based on data from previous clinical studies, treatment with fostamatinib may be associated with lowering of ANC.

A decrease in ANC may require adjustment of the dose of study drug. Follow the dose adjustment guidelines as outlined below when adjusting the dose of study medication.

Dose Adjustment

Dose	Dose Level -1	Dose Level -2	Dose Level -3[a]	Dose Level -4[a]
100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue	----
150 mg PO *bid*	100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue

[a] The Sponsor's Medical Monitor should be consulted prior to consideration of dose modification to levels -3 or -4.

Decrease in ANC to < 1,000/µL:

- Repeat ANC within 72 hours.
- If repeat testing confirms that ANC is < 1,000/µL, immediately interrupt study drug administration.
    - Repeat ANC at 72 hour intervals.
- When ANC recovers to > 1,500/µL, restart study drug at dose level -1.

Second event of ANC < 1,000/µL:

- Confirm ANC as above.
- If confirmed, immediately interrupt study drug until ANC > 1,500/µL.
- Restart study drug at dose level -2.

Appendix 3: Management of Diarrhea

Diarrhea

- Based on data from previous clinical studies, treatment with fostamatinib may be associated with diarrhea.
- Subjects should be made aware that they may experience diarrhea and instructed to contact the clinical site if they experience diarrhea.
- Careful monitoring, and early, **aggressive treatment** of diarrhea will ensure that severe complications such as dehydration are avoided.
- In some circumstances it may be necessary to adjust the dose of study drug. Follow the dose adjustment guidelines outlined below when adjusting the dose of study medication.

Dose Adjustment

Dose	Dose Level -1	Dose Level -2	Dose Level -3[a]	Dose Level -4[a]
100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue	----
150 mg PO *bid*	100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue

a The Sponsor's Medical Monitor should be consulted prior to consideration of dose modification to levels -3 or -4.

Grading of Severity of Diarrhea: The US National Cancer Institute has introduced the following criteria for the grading of severity of diarrhea: [(7)]

- **Grade 1**: Increase of less than 4 stools per day over baseline
- **Grade 2**: Increase of 4 to 6 stools per day over baseline, not interfering with activities of daily living (ADL)
- **Grade 3**: Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; interference with self-care ADL
- **Grade 4**: Life-threatening consequences; urgent intervention indicated
- **Grade 5**: Death

Grade 1 or 2 Diarrhea

- Study drug may be continued.
- Discontinue all laxatives.
- Subjects should be instructed to drink 8-10 glasses of water or clear fluids per day.
- Subjects should be encouraged to make dietary changes including elimination of dairy products and eating smaller but more frequent meals.

- Consider stool sample for microbiologic evaluation and antibiotics if subject is neutropenic.
- Grade 1, consider initiating treatment with loperamide according to the regimen below. Grade 2, initiate treatment with loperamide according to the regimen below:
    - 4 mg loperamide initial dose.
    - 2 mg loperamide after each subsequent loose stool.
    - Not to exceed a maximum of 20 mg (10 tablets) in 24 hours.
- Subjects with persistent diarrhea (> 48 hours) should be monitored carefully for dehydration and electrolyte imbalance.

Grade 3 or 4 Diarrhea

- The subject should be instructed to immediately interrupt study drug.
- Initiate aggressive fluid replacement to treat potential dehydration.
- Consider stool sample for microbiologic evaluation and antibiotics if subject is neutropenic.
- Begin treatment with loperamide and continue treatment until the diarrhea has resolved:
    - 4 mg loperamide initial dose.
    - 2 mg loperamide after each subsequent loose stool.
    - Not to exceed a maximum of 20 mg (10 tablets) in 24 hours.
- When diarrhea improves to ≤ Grade 1, restart study drug at dose level -1.

Management of Second Event of Grade 3 and 4 Diarrhea

- Immediately interrupt study drug administration.
- Initiate aggressive fluid replacement to treat potential dehydration.
- Consider stool sample for microbiologic evaluation and antibiotics if subject is neutropenic.
- Begin treatment with loperamide and to continue treatment until the diarrhea has been resolved:
    - 4 mg loperamide initial dose.

  - 2 mg loperamide after each subsequent loose stool.
  - Not to exceed a maximum of 20 mg (10 tablets) in 24 hours.
- When diarrhea improves to ≤ Grade 1, restart study drug at dose level -2.

Source: Yang 2013 [2]

Appendix 4: Management of Hypertension

Treatment with fostamatinib may cause blood pressure elevation in certain subjects. It is believed that this effect is a result of off-target activity against the VEGFR2 receptor. Increases in BP have proven to be amenable to treatment, generally without a requirement for study drug interruption. **Subjects with elevated blood pressure should receive prompt treatment**.

Blood pressure for all subjects should be kept below 140/90 mmHg; for subjects with increased cardiovascular risk, diabetes or renal insufficiency consideration should be given to maintaining the blood pressure below 130/80 mmHg.

In previous clinical studies evaluating fostamatinib, the following antihypertensive agents have proven effective in managing BP:

- Calcium channel blockers
- Angiotensin converting enzyme inhibitors
- Angiotensin receptor blockers
- Beta-blockers

If aggressive and appropriate anti-hypertensive therapy does not control BP (< 140/90), it may be necessary to reduce the dose of study medication.

Management Algorithm for Elevated Blood Pressure

Follow the dose adjustment guidelines below when adjusting the dose of study medication.

Dose Adjustment

Dose	Dose Level -1	Dose Level -2	Dose Level -3[a]	Dose Level -4[a]
100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue	----
150 mg PO *bid*	100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue

a The Sponsor's Medical Monitor should be consulted prior to consideration of dose modification to levels -3 or -4.

The following should result in prompt discontinuation of study medication:

- The subject becomes symptomatic due to blood pressure elevation.
- The blood pressure cannot be brought under control despite best efforts at blood pressure management.

If BP ≥ 180/110 mmHg at any time after randomization:

- Immediately interrupt study drug administration.
- Initiate or increase anti-hypertensive medication.
- Reassess BP twice weekly.
- If repeat BP ≥ 180/110 mmHg despite anti-hypertensive treatment, discontinue study drug.
- Increase anti-hypertensive medications until control is established.
- Restart study drug when blood pressure < 140/90 mm Hg.

If the BP is found to be 160-179 systolic or 100-109 diastolic at any visit after randomization:

- Continue study drug at assigned dose level.
- Initiate or increase anti-hypertensive therapy immediately.
- Reassess BP twice weekly.
- If, after 1 week, the BP remains ≥ 160-179 systolic or≥ 100-109 diastolic despite aggressive antihypertensive therapy, interrupt study drug administration.
- Increase anti-hypertensive medications until control is established.
- Restart study drug when blood pressure < 140/90 mmHg.

If BP is ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic but below 160 systolic or 100 diastolic at any visit after randomization:

- Continue study drug at assigned dose level.
- Repeat blood pressure assessment within 1 week.
- If blood pressure remains above ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic after 1 week initiate or increase antihypertensive therapy immediately.
- Continue to monitor BP weekly until control is established.
- If BP remains ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic for more than 8 weeks, despite aggressive antihypertensive therapy, reduce dose of study drug to dose level -1.

Source: Maitland 2010 [8]

Appendix 5: SF-36 Questionnaire

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g Walking more than a mile	☐ 1	☐ 2	☐ 3
h Walking several hundred yards	☐ 1	☐ 2	☐ 3
i Walking one hundred yards	☐ 1	☐ 2	☐ 3
j Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

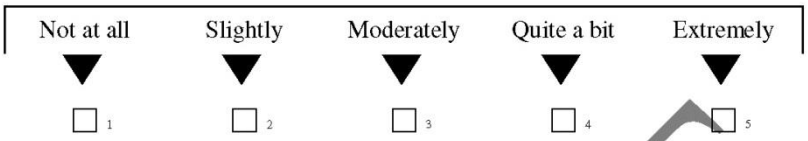
4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

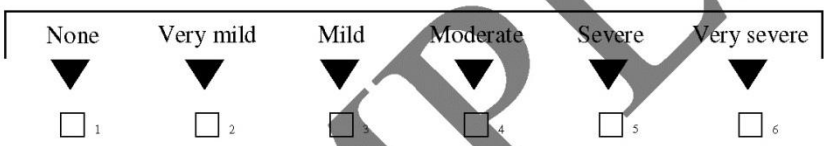
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

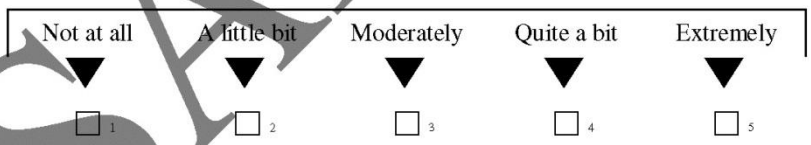
6. **During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?**



7. **How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?**



8. **During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?**



9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 6: Karnofsky Performance Status Scale

Scale (%)	Description
100	Normal; no complaints (ECOG 0)
90	Able to carry on normal activities; minor signs or symptoms of disease (ECOG 0)
80	Normal activity with effort (ECOG 1)
70	Cares for self; unable to carry on normal activity or do active work (ECOG 1)
60	Requires occasional assistance but able to care for most of his/her needs (ECOG 2)
50	Requires considerable assistance and frequent medical care (ECOG 2)
40	Disabled: requires special care and assistance (ECOG 3)
30	Severely disabled; hospitalization indicated, though death not imminent (ECOG 3)
20	Very sick; hospitalization necessary; active supportive treatment necessary (ECOG 4)
10	Moribund (ECOG 4)
0	Dead

Source: Karnofsky 1949 [3]

Appendix 7: The Immune Thrombocytopenic Purpura Bleeding Score Assessment

	Bleeding Score		
Site	**0**	**1**	**2**
Skin (Physical Examination (PE))	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (PE)	None	1 blood blister or >5 petechiae or gum bleeding that clears easily with rinsing	Multiple blood blisters and/or gum bleeding
Skin (Hx)	None	1–5 bruises and/or scattered petechiae	>5 bruises with size >2 cm and/or diffuse petechiae
Oral (Hx)	None	1 blood blister or >5 petechiae and/or gum bleeding <5 min	Multiple blood blisters and/or gum bleeding >5 min
Epistasis	None	Blood when blowing nose and/or epistaxis <5 min (per episode)	Bleeding >5 min (per episode)
Gastrointestinal (GI)	None	Occult blood	Gross blood
Urinary (U)	None	Microscopic (+ve dipstick)	Macroscopic
Gynecological (GYN)	None (normal period)	Spotting not at time of normal period	Bleeding >spotting not at time of period or very heavy period
Pulmonary	None	N/A	Yes
Intracranial hemorrhage	None	N/A	N/A
Subconjunctival hemorrhage	None	Yes	N/A

Source: Page 2007 [4]

Appendix 8: World Health Organization Bleeding Scale

0 – No bleeding

1 – Petechiae

2 – Mild blood loss

3 – Gross blood loss

4 – Debilitating blood loss

Source: Miller 1981 [10]

Appendix 9: Restricted Medications

Subjects taking fostamatinib may be affected by drug-drug interactions.

Fostamatinib is metabolized by CYP3A4. In the presence of a strong inhibitor of CYP3A4, the systemic exposure of the active metabolite of fostamatinib may be increased significantly. **Strong inhibitors of CYP3A should not be co-administered with fostamatinib**. Inducers of CYP3A4 may lower concentrations of active drug, possibly to subtherapeutic concentrations; their use in subjects taking fostamatinib should be limited.

Fostamatinib is an *in vitro* inhibitor of P-glycoprotein and affects digoxin bioavailability by inhibiting P-gp. If a subject requires digoxin or is taking digoxin concurrently with fostamatinib, digoxin levels should be monitored carefully according to local practice, as the digoxin dose may need to be lowered.

Fostamatinib is known to increase the plasma concentration of the HMG-CoA reductase inhibitors simvastatin and rosuvastatin by 50-100%. Subjects should have their dose of HMG-CoA reductase lowered and lipid response (CPK, clinical signs) followed closely to monitor for any adverse effects associated with higher concentrations, including myositis.

Subjects' concomitant medications should be examined for additional possible drug-drug interactions. The list below is not an exhaustive list (the Sponsor's Medical Monitor should be consulted in the event of questions).

List of Inhibitors and Inducers of CYP3A4

Strong Inhibitors of CYP3A4

Clarithromycin	Telithromycin	Ketoconazole
Itraconazole	Fluvoxamine	Nefazodone
Ritonavir	Indinavir	Nelfinavir
Sequinavir	Atazanavir	

Moderate Inhibitors of CYP3A

Amiodarone	Aprepitant	Erythromycin
Troleandomycin	Fluconazole	Imatinib
Verapimil	Diltiazem	Amprenavir
Fosamprenavir	Grapefruit juice	Seville oranges
Star fruit		

CYP3A Inducers

Barbiturates	Efavirenz	Nevaripine
Pioglitazone	Rifampin	Rifabutin
Carbamazepine	Phenytoin	Modafinil
St. John's Wort		

Appendix 10: Post Database Lock Extension

After the final database lock, patients who continue to receive study drug will be cared for according to local clinical practice. All visits required in the original protocol must be completed and the data reported in the EDC. Protocol changes made after database lock must be approved by the Sponsor. The information in this section will not be provided to all Investigators; but rather to Investigators who continue to treat patients with study drug.

Patients will receive the same dose of study drug that the investigator has determined provided clinical benefit before database lock. The dose may be adjusted down during this period but cannot be adjusted to a dose higher than 150 mg PO BID, and only if this dose level was previously well tolerated. No more than 6 months of study drug will be dispensed at any one time. Treatment on this extension may continue for up to 12 months if the patient is tolerating study drug, has not withdrawn from the study, and is considered by the investigator to continue to receive clinical benefit.

After the final database lock, for patients who continue to receive study drug, the following information will be recorded in the patient chart (unless otherwise directed) according to local practice:

- Concomitant medication use
- Study drug dispensing/accountability on the Drug Accountability Log
- AEs and SAEs.
    - SAEs must be reported to the Sponsor on the Rigel SAE form as described in Section 9.2.3 including information relevant to SAE interpretation (eg, concomitant medications or laboratory values [local testing]). The sponsor will advise the Investigator or study site personnel on how to proceed in the event of an SAE. The IB is the reference document used for the definition of expectedness/listedness.
- The date and reason for patient withdrawal from the study

Final study visit procedures will not be conducted for patients who continue to receive study drug. On-site monitoring will be limited, and only SAEs will be collected after the final database lock. Completion of eCRFs will no longer be required as no further analysis or data validation will be performed. Also, the SAEs will not be integrated in any integrated analysis that may be performed.