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CLINICAL PROTOCOL

A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Study of Fostamatinib Disodium in the Treatment of Warm Antibody Autoimmune Hemolytic Anemia

Protocol Number:	C-935788-057
EudraCT Number:	2018-004774-97
Study Sponsor:	Rigel Pharmaceuticals, Inc. 1180 Veterans Boulevard South San Francisco, CA 94080 USA Tel: +1.650.624.1100
Sponsor Representative:	[redacted]
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	[redacted]
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Version 4.1:	30 June 2020
Version 5.0:	05 March 2021
Version 6.0:	04 February 2022

Confidentiality Obligation

The information contained in this protocol and all information and data related to R935788 ("Drug") are the confidential and proprietary information of Rigel Pharmaceuticals, Inc. ("Rigel") and may not be disclosed to others without prior written permission of Rigel. The Investigator may, however, disclose information about this protocol and Rigel's Drug to individuals under his/her supervision who are working on the protocol, provided such individuals are bound by written agreement to maintain the confidentiality of such information. The Investigator may disclose information about the Drug as required by applicable law, provided he/she promptly notifies Rigel.

Sponsor Signature for Protocol C-935788-057

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, Clinical Trial Agreement, ICH Guidelines for Good Clinical Practice (E6, R2), Declaration of Helsinki (1996), and applicable laws and regulations.

_____ _____

Date

[redacted]
Senior Medical Director
Rigel Pharmaceuticals, Inc.

Signature of Agreement for Clinical Protocol C-935788-057

I agree to the following:

- To conduct the study in strict accordance with this Clinical Trial Agreement, ICH Guidelines for Good Clinical Practice (E6, R2), Declaration of Helsinki (1996), and applicable laws and regulations.
- To maintain adequate and accurate records and to make those records available for inspection by Rigel (or its authorized representative), the US Food and Drug Administration (FDA), or any other Regulatory Agency authorized by law.
- To report to Rigel (or its authorized representative) any adverse events (AEs) or serious adverse events (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** (DDMMMYYYY)
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, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Study of Fostamatinib Disodium in the Treatment of Warm Antibody Autoimmune Hemolytic Anemia

Objectives:

- The primary objective of this study is to compare the proportion of warm antibody autoimmune hemolytic anemia (wAIHA) subjects who achieve a durable hemoglobin response between the fostamatinib and placebo groups.
- The secondary objectives of this study are:
    1. To compare the proportion of subjects with hemoglobin response on at least one visit between the fostamatinib and placebo groups.
    2. To compare the proportion of subjects who achieve a change from Baseline in hemoglobin level of ≥ 2 g/dL between the fostamatinib and placebo groups.
    3. To compare the change in hemoglobin value from Baseline to the End of Treatment between the fostamatinib and placebo groups.
    4. To compare the proportion of subjects who use permitted rescue medications after Week 4 between the fostamatinib and placebo groups.
    5. To compare the change from Baseline to Week 24 in Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-F).
- The safety objective is to assess the safety of fostamatinib in subjects with wAIHA.
- Additional efficacy and pharmacoeconomic objectives will compare the fostamatinib and placebo groups for the endpoints noted in Section 4.5.

Methodology:

This is a Phase 3 multi-center, randomized, double-blind, placebo-controlled, parallel group study to investigate the efficacy of 24 weeks of treatment with fostamatinib (R935788) vs. placebo in achieving a durable hemoglobin response in subjects with wAIHA who have failed at least one prior treatment regimen.

After qualifying for the study, approximately 90 subjects will be randomized in a 1:1 ratio to 1 of 2 treatment groups: fostamatinib 100 mg by mouth (PO) twice daily (*bid*), or matching placebo. Subjects will self-administer the study drug in the morning and evening throughout the 24-week treatment period. Randomization will be stratified by concomitant steroid use at Baseline (≥20 vs. <20 mg daily) and by severity of anemia at screening (hemoglobin <9 vs. ≥9 g/dL).

Treatment Group	Number of Subjects	Study Drug	Regimen
A	45	Placebo	*bid* (morning and evening)
B	45	Fostamatinib	*bid* (morning and evening)

- Starting at Week 4, the initial fostamatinib dose of 100 mg PO *bid* or matching placebo will be increased to fostamatinib 150 mg PO *bid* or matching placebo if subjects have adequately tolerated the study drug in the investigator's judgment.
- The dose may be reduced at any time to a dose as low as fostamatinib 100 mg PO once daily (*qd*) or matching placebo if dose-limiting adverse events are observed per the dose adjustment table below.

Dose Adjustment

Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3	Dose Level -4
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

- Over the course of the study, subjects will be expected to visit the clinic approximately 15 times. Safety assessments and hemoglobin levels will be performed at each visit to evaluate the safety and efficacy of study drug (fostamatinib or placebo), and to determine if a dose adjustment is required. The end of the study will be when the last subject has completed either the Week 24 visit or their last follow-up study visit, whichever is later.
- Subjects who have completed this study will be encouraged to enroll into an open-label extension study with fostamatinib. Subjects and investigators will remain blinded to the C-935788-057 treatment assignment at the time of enrollment in the extension study. Details of the dosing strategy during the open-label extension will be specified in a separate protocol.
- **Allowed AIHA Therapies:**
- Subjects may continue concurrent steroid therapy and other wAIHA therapy (maximum of 2 therapies) as listed below throughout their participation in the study (note: throughout this document the term 'steroid' indicates corticosteroid drugs as well as glucocorticoids). If an allowed medication is discontinued during screening, the interval between last dose of medication and randomization is per the timelines listed in the table below:

Medication	Number of weeks required to be at stable dose prior to randomization	Minimum required interval between discontinuation and randomization
Azathioprine	4 weeks	4 weeks
Steroids, including dexamethasone	2 weeks	2 weeks
Erythropoiesis-stimulating agents	4 weeks	4 weeks
Mycophenolate Mofetil	4 weeks	4 weeks
Dapsone	4 weeks	4 weeks
Danazol	4 weeks	4 weeks

- Doses and regimens of concurrent wAIHA therapies allowed at entry may not be changed during the 24-week treatment period except for temporary steroid dose increases instituted as rescue therapy or a steroid taper as allowed by the protocol (see below).
- If Promacta is being given as a concurrent medication, the dose must be stable for 4 weeks prior to randomization.
- Other medications when prescribed for wAIHA (e.g. rituximab or other anti-CD20 monoclonal antibody, cyclosporine, ibrutinib or other BTK inhibitor, chemotherapy agents such as cyclophosphamide, vincristine, investigational agents for AIHA, etc.), are not allowed during study treatment (from Day 1 until the last dose of study drug).
- Subjects requiring any AIHA therapies other than those allowed or an escalation of the allowed medications other than steroids should be withdrawn from the study. The Medical Monitor should be consulted in these instances.

Rescue Protocol:

Use of rescue medications including increases in steroid dose should be avoided for the duration of the study unless medically necessary. Rescue may be given following a decrease in Hgb of >1.5 g/dL from baseline **OR** new or worsening symptoms of anemia, so long as urgent treatment is required in the judgment of the investigator. In subjects meeting these criteria, the following rescue regimens are permitted:

1. Increase or initiate steroid dose up to 80 mg/daily prednisone (or equivalent) for approximately 2 weeks or until clinically stable, then taper the dose by 10 to 20 mg prednisone (or equivalent) per week until return to baseline dose level;
2. IV methylprednisolone up to 1 g/day x 1 day up to 3 days;
3. Oral dexamethasone up to 40 mg/day x up to 4 days;
4. Red blood cell (RBC) transfusion;
5. IVIg: up to 1g/kg x 1 day up to 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. The use of any rescue therapy regimen not noted above is not permitted. Only the rescue regimens above are allowed.

Steroid Taper Protocol:

For subjects who have reached Week 12, achieved a durable response (see definition below for durable response), and have had at least 2 subsequent *scheduled* visits with hemoglobin assessments showing continued response, a steroid taper may be considered.

The steroid taper may be considered as follows:

- If the dose is above 20 mg/day prednisone (or equivalent), decrease dose level by 10 mg* (or equivalent) every other week, until the dose level is 20 mg/day prednisone (or equivalent). Then decrease the dose by 5 mg increments every other week until the dose is 10mg/day and maintain.
- The taper may be suspended at any dose level to maintain the hemoglobin response and as needed for subject safety (e.g., to avoid adrenal insufficiency).

- If a decrease in hemoglobin of ≥0.5 g/dL is observed at any subsequent visit (as compared to either the last hemoglobin obtained prior to initiating the taper OR the previous hemoglobin assessment), the current steroid dose level should be maintained and the hemoglobin repeated in 3 days to assure no recurrence of hemolysis. A sustained (at least 2 consecutive hemoglobin results) decrease in hemoglobin of ≥1.0 g/dL should prompt a re-escalation of prednisone (or equivalent) dose to the previous, higher dose level.
- If the steroid dose is 10 mg/day prednisone (or equivalent) or below, no steroid tapering is allowed in this study.

* If the steroid dose is 25 mg/day of prednisone or equivalent, decrease the dose by 5 mg increments to 10 mg/day and maintain. For example, if the dose is 35 mg/day of prednisone or equivalent (or higher dose that is a multiple of 5), decrease the dose in 10 mg increments as described above to 25 mg/day for 2 weeks; then decrease in 5 mg increments to 10 mg/day and maintain.

Consideration of a steroid taper is to be discussed with the Medical Monitor prior to initiating any changes.

Endpoints:

Primary Efficacy Endpoint:

The primary efficacy endpoint is achievement of durable hemoglobin response (Yes/No) defined as achieving a hemoglobin level ≥ 10 g/dL with an increase from Baseline in hemoglobin level of ≥ 2 g/dL on 3 consecutive available visits during the 24-week treatment period, in which hemoglobin measurements eligible for this definition occurred outside a Rescue Treatment Visit Exclusion Period.

Secondary Efficacy Endpoints:

The secondary efficacy endpoints within the 24 weeks of treatment are:

1. Hemoglobin response on at least one visit (Yes/No)
2. Achievement of a change from Baseline in hemoglobin level of 2 g/dL or greater (Yes/No)
3. Change in hemoglobin value from Baseline to End of Treatment (Week 14 to Week 24)
4. Use of permitted rescue medications after Week 4 (Yes/No)
5. Change from Baseline to Week 24 in FACIT-F

Additional efficacy will be evaluated and detailed in the SAP.

Safety Endpoints:

The following safety endpoints will be evaluated:

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Incidence and severity of TEAEs of interest

- Change from Baseline for select laboratory tests over time (e.g., hematology, chemistry)
- Change from Baseline in blood pressure over time
- Change from Baseline in absolute neutrophil count (ANC) over time
- Change from Baseline in liver function tests (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST]), total bilirubin, direct and indirect bilirubin) over time.

Pharmacokinetic Endpoints:

Plasma concentration of the active component of fostamatinib (R406) relative to the date and time of last dose of study drug, at Weeks 2, 4, 12 and 18 of the treatment period.

Number of Subjects: Approximately 90 subjects (45 fostamatinib and 45 placebo) will be enrolled at multiple international sites.

- **Study Population**: Patients with warm antibody autoimmune hemolytic anemia (wAIHA).

For the purpose of this study, the term 'subject' will refer to patients with warm antibody autoimmune hemolytic anemia (wAIHA) 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 undergoing any study-specific procedures.
2. Subject must have a diagnosis of primary or secondary wAIHA as documented by a positive direct antiglobulin test (DAT) specific for anti-IgG or anti-IgA. Eligibility may be based on a historical DAT obtained within 12 months of the screening visit from a local laboratory, provided that specific IgG or IgA positivity is documented; otherwise, this assay will be done at screening by a central laboratory.
3. Has failed or not tolerated at least one prior wAIHA treatment, e.g., steroids, rituximab, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil (MMF), danazol, vincristine, ESA or splenectomy (folate, iron or other supplements do not fulfill this criterion).
4. Has haptoglobin <LLN **or** total bilirubin >ULN **or** lactate dehydrogenase (LDH) >ULN.
5. At screening, subject's hemoglobin level must be ≤9 g/dL

   OR

   If the hemoglobin value is >9 g/dL and <10 g/dL, subject must be on an allowed wAIHA treatment (see Allowed AIHA Therapy table) AND the subject must have documented symptoms related to anemia (e.g., weakness, dizziness, fatigue, shortness of breath, chest pain).
6. Male or female at least 18 years of age at screening.
7. Karnofsky performance status (KPS) ≥70.

8. Subject's concurrent treatment for wAIHA may consist of no more than two of any of the following agents: azathioprine, steroids, ESAs, mycophenolate mofetil, dapsone or danazol at a stable dose, as defined in the Allowed AIHA Therapies table. Subject has not taken any disallowed therapies in the intervals defined by the protocol.
9. Female subjects must be either post-menopausal for at least 1 year or surgically sterile; or, if of childbearing potential, must not be pregnant or lactating and must agree to use a highly effective 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 screening, an intrauterine device (IUD), or intrauterine hormone-releasing system (IUS), or true abstinence (i.e. abstinence is in line with the preferred and usual lifestyle of the subject.)
10. 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. Subject with other types of AIHA (e.g., cold antibody AIHA, cold agglutinin syndrome, mixed type AIHA, or paroxysmal cold hemoglobinuria).
2. Subject has AIHA secondary to autoimmune disease, including systemic lupus erythematosus (SLE), or lymphoid malignancy if the underlying disease is not stable or is not well-controlled on current therapy, per investigator medical judgment.
3. Subject has a history of or active, clinically significant, cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, psychiatric, musculoskeletal, genitourinary, dermatological, or other disorder that, in the investigator's opinion, could affect the conduct of the study or the absorption, metabolism or excretion of the study drug.
4. Subject has uncontrolled or poorly controlled hypertension, defined as systolic blood pressure ≥135 mmHg or diastolic blood pressure ≥85 mmHg, whether or not the subject is receiving anti-hypertensive treatment.
5. Subject has one or more of the following laboratory abnormalities at screening: neutrophil count of <1,000/µL or platelet count of <30,000/µL, unless due to Evans syndrome; transaminase levels (i.e., alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >1.5 x ULN.
6. Has documented HIV infection or active hepatitis B or hepatitis C infection.
7. Subject is currently enrolled in an investigational drug or device study or has used an investigational drug or device within 30 days or 5 half-lives (whichever is longer) of Day 1.
8. In the judgment of the Investigator, the subject may not be able to fully comply with study requirements.
9. Subject has been treated with fostamatinib previously for any indication.

10. Subject has a known allergy and/or sensitivity to the test article or its components.
11. Subject has had a splenectomy within the past 4 weeks.

Disallowed AIHA Therapies: Any of the disallowed therapies below may not be taken within the indicated interval prior to Day 1.

Drug	**Prohibited Period Prior to Day 1** (from last dose of agent)
RBC transfusion	7 days
IVIg	14 days
Cyclosporine	30 days
Rituximab or other anti-CD20 monoclonal antibody	8 weeks
Ibrutinib or other BTK inhibitor	4 weeks
Chemotherapy agents, e.g. cyclophosphamide, vincristine	6 weeks
Investigational agent	30 days or 5 half-lives, whichever is greater

Investigational Product: Fostamatinib disodium (R935788) and matching placebo

Route of Administration: Oral

Dose: Initial dose of fostamatinib will be 100 mg or matching placebo *bid*.

Starting at Week 4, the initial fostamatinib dose of 100 mg PO *bid* or matching placebo will be increased to fostamatinib 150 mg PO *bid* or matching placebo if subjects have adequately tolerated the study drug, based on the Investigator's judgment.

The dose may be reduced at any time to a dose as low as fostamatinib 100 mg PO *qd* or matching placebo if dose limiting adverse events are observed.

Duration of Treatment: 24 weeks (extended treatment available to eligible subjects under a separate protocol).

Statistical Methods:

Determination of Sample Size:

The sample size is based on the number of subjects necessary to demonstrate efficacy in the primary endpoint: achievement of durable hemoglobin response (Yes/No). In a previous phase 2 study, approximately 27% of subjects (7 out of 26) treated with fostamatinib achieved a durable response.

No data are available on placebo response rates for this population. It is expected that no more than approximately 5% of placebo subjects would achieve a durable hemoglobin response. Under these assumptions, a sample size of 90 subjects (i.e., 45 subjects per treatment group)

will yield at least 84% power to detect a difference between the 2 groups at the 0.05 two-sided significance level using Fisher's exact test.

Analysis of the Primary Efficacy Endpoint:

Analysis of the primary efficacy endpoint will be performed using Cochran-Mantel-Haenszel (CMH) test stratified by concomitant steroid use at Baseline (≥ 20 vs. < 20 mg daily), and screening hemoglobin level (< 9 vs. ≥ 9 g/dL). The odds ratio will be presented along with the 95% CI. The study will be considered to meet its primary efficacy objective if the lower bound of the 95% CI of odds ratio of durable hemoglobin response between the Fostamatinib and Placebo treated subjects is greater than 1.

In addition, the exact Clopper-Pearson 95% CI for the proportions and the Agresti-Min exact unconditional CI for the difference in proportions will be estimated.

The difference in proportion of durable hemoglobin response between the two treatment groups will be estimated and the 95% Miettinen-Nurminen score CIs will be computed taking into account the stratification factors.

Sensitivity analysis for primary endpoint will be evaluated using subgroup prognostic, multiple imputation for missing data, and a washout of 6 weeks for rescue treatment exclusion period.

Analysis of Secondary Efficacy Endpoints:

Analysis of binary secondary efficacy endpoints (hemoglobin response on at least one visit, achievement of a change from Baseline in hemoglobin level of 2 g/dL or greater, use of permitted rescue medications after Week 4) will be performed using the CMH test stratified by concomitant steroid use at Baseline (≥ 20 vs. < 20 mg daily), and Screening hemoglobin level < 9 vs. ≥ 9 g/dL). In addition, the exact Clopper-Pearson 95% CI for the overall proportions will be estimated by treatment group. In addition, the Agresti-Min exact unconditional 95% CI for the difference in proportions will be estimated as well as the 95% Miettinen-Nurminen score CIs taking into account the stratification factors.

Change from Baseline to End of Treatment in hemoglobin levels will be analyzed using an analysis of variance (ANOVA) model with multiple imputations with concomitant steroid use at Baseline (≥ 20 vs. < 20 mg daily), screening hemoglobin level (< 9 vs. ≥ 9 g/dL) and treatment group as fixed effect in the model. The missing hemoglobin values will be imputed. Least squares mean with the 95% CI for the mean will be constructed for each treatment group and for the differences between the treatment groups.

Change from Baseline to Week 12 and Week 24 in the FACIT-F will be analyzed using Mixed effect model for repeated measures implemented by SAS PROC MIXED. The model will use change from Baseline in FACIT-F as a response variable and include the fixed categorical effects of treatment group, weeks (12 and 24), interaction between treatment and weeks, concomitant steroid use at Baseline (≥ 20 vs. < 20 mg daily), Screening hemoglobin level (< 9 vs. ≥ 9 g/dL), and Baseline FACIT-F as a covariate.

Safety Analysis

Safety will be assessed by examination of TEAEs, TEAEs of interest, extent of exposure, and changes from Baseline in laboratory values (e.g., selected hematology, chemistry) over time.

Furthermore, changes in vital signs of pulse, blood pressure, temperature, and body weight will be monitored.

Pharmacokinetic Analysis:

Plasma concentrations of the active component of fostamatinib (R406) will be measured at Weeks 2, 4, 12, and 18. The timing of the PK sampling as well as the date, time, and dosage of the last dose of study drug will be recorded. Data will be summarized by visit in accordance with the administered dose and regimen. Descriptive statistics (n, mean, standard deviation, median, minimum, IQR) will be tabulated.

Independent Data Monitoring Committee:

An independent DMC will be formed and constituted according to appropriate regulatory agency guidelines. The independent DMC will review safety data periodically and provide recommendations according to the charter. Detailed information regarding the composition of the committee and its procedures will be provided in the DMC charter.

2.0 ABBREVIATIONS AND TERMS

AE	adverse event
AIHA	autoimmune hemolytic anemia
ALT	alanine aminotransferase
ANC	absolute neutrophil counts
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BCRP	breast cancer resistant protein
bid	*bis in die* (twice daily)
BL	bilirubin
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	United States Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CRO	Contract Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAT	direct antiglobulin test
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue scale
FcR	Fc receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GI	Gastrointestinal
h	hour
HBV	hepatitis B virus
HCV	hepatitis C virus
HEENT	head, eye, ear, nose, and throat
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IgA	immunoglobulin A
IgG	immunoglobulin G
IRB	Institutional Review Board
ITP	immune thrombocytopenic purpura
IV	Intravenous
IVIg	Intravenous IgG
kg	kilogram
KPS	Karnofsky performance status
L	liter
LDH	lactate dehydrogenase
LFT	liver function tests
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
mg	milligram
MPV	mean platelet volume
OATP	organic anion transporter protein
PD	pharmacodynamic
P-gp	p-glycoprotein
PK	pharmacokinetic
PO	*per os* (by mouth)
PP	per protocol
qd	*quaque die* (once daily)

R406	Rigel compound R940406
R788	Rigel compound R935788 (fostamatinib)
RA	rheumatoid arthritis
RBC	red blood cell
RDW	red blood cell distribution width
RTSM	Randomization and Trial Supply Management
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
Syk	spleen tyrosine kinase
TEAE	treatment-emergent adverse events
T_{max}	time of maximum plasma concentration
ULN	upper limit of normal
wAIHA	warm autoimmune hemolytic anemia
WBC	white blood cell
WHO	World Health Organization
UGT	uridine 5'-diphospho-glucuronosyltransferase
x ULN	multiple of upper limit of normal

3.0 INTRODUCTION

3.1 Background

Autoimmune hemolytic anemia (AIHA) is an acquired disorder manifested by autoantibody-mediated red blood cell (RBC) destruction. The estimated incidence is 0.8-3 per 100,000/year with a mortality rate of 11%.[1] AIHA is subclassified as either warm or cold, some 80% of cases are warm AIHA, and can be either primary or secondary to an underlying disease such as autoimmune disease, 20%, lymphoproliferative disorder, 20%, or infections and tumors. [1]

The diagnosis of AIHA is typically made when hemolysis is associated with a positive direct antiglobulin test (DAT), indicating that RBC autoantibodies and/or complement proteins are bound to red cells. Additional abnormalities include a reduced serum haptoglobin level, an increased indirect bilirubin, and an elevated lactate dehydrogenase (LDH). [2, 3]

The first-line treatment of AIHA generally consists of steroids. Up to 85% of patients will respond, however fewer than 20% of patients will be cured. Splenectomy has traditionally been the second line therapy of choice for this disease, with 60-70% of patients having a sustained response. Other therapeutic approaches that can be used, following the failure of front-line treatment, include rituximab, IVIg, cyclosporine, mycophenolate mofetil, azathioprine, and cyclophosphamide. The availability of these alternative therapies has challenged the role of splenectomy as the preferred second-line treatment.[1, 4-6]

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

Aggregation of the Fc receptors, induced by antibody-antigen complexes, can activate 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. FcRγ have been implicated in immune destruction of RBCs. Accelerated clearance of circulating IgG-coated RBCs via FcRγ-bearing macrophages in the spleen and liver is believed to be a pathogenic mechanism in AIHA.[2] Fostamatinib (R788) is the prodrug of R940406 (R406), a potent and relatively selective inhibitor of Syk and, consequently, of the FcR and BCR signaling pathways. R406 inhibits Syk and FcR signaling at concentrations generally achieved with fostamatinib doses of 100-150 mg twice daily (*bid*) and above, and nonclinical data have affirmed its activity in AIHA.

3.2 Nonclinical Studies

Podolanczuk et al. reported on preclinical studies of R788/R406 in murine models of immune thrombocytopenic purpura (ITP) and AIHA.[7] Mice injected with an antibody directed to RBCs (anti-Ly76) were anemic 24 hours post injection. Mice treated with vehicle alone displayed no protection, while mice treated with either 25 or 40 mg/kg R788 were significantly protected from anemia.

Figure 1: Mice Treated with R788 Following Induction of Anemia by Administration of Anti-erythrocyte Antibody (TER119)

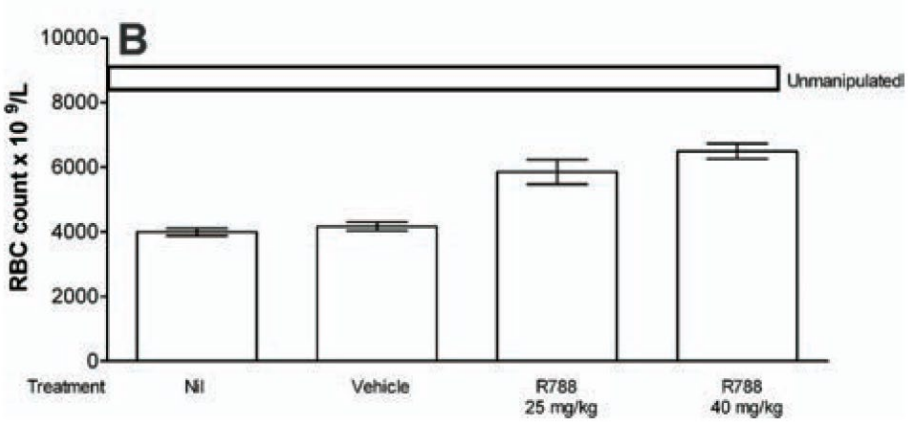


Figure 1 shows data for CD1 mice that were pretreated with nothing (Nil), vehicle, or R788 (at the dose indicated) on Day 1. Mice in the vehicle and R788 groups were injected again (8 hours apart) on Day 2. All mice except for the unmanipulated group were injected with anti-erythrocyte (TER119) antibody on Day 2 to induce anemia. Mice were bled on Day 3 for RBC count. All data are expressed as mean ± SEM (n = 6 mice per group). [8]

3.3 Fostamatinib Pharmacokinetics, Efficacy and Safety

3.3.1 Pharmacokinetics

Fostamatinib (R788) is a prodrug rapidly converted in the gut to R406. R406 appears rapidly in the systemic circulation after fostamatinib dosing. Peak plasma R406 concentration is usually achieved approximately 1.5 hours post dose (t_{max}). Negligible levels of R788 are found in plasma. The terminal half-life of R406 is approximately 15 hours. In general, exposure of R406 (AUC, C_{max}) increases in a dose proportional manner up to 200 mg *bid*. Administration of fostamatinib with a high-calorie, high-fat meal modestly increases R406 AUC by 23% and C_{max} by 15%, indicating fostamatinib can be given with and without food. In *in vitro* studies, R406 is about 98.3% protein bound in human plasma. The red blood cell to plasma concentration ratio is approximately 2.6. The apparent volume of distribution at steady-state (V_{ss}) and total clearance (CL) of R406 is approximately 256 L and 15.7 L/h, respectively; suggesting the drug is well distributed in the body and cleared at a moderate rate.

Population analyses of PK data from healthy subjects and in patients with rheumatoid arthritis (RA) and idiopathic thrombocytopenic purpura (ITP) indicate fostamatinib pharmacokinetics (PK) is not altered by age, sex, or race/ethnicity. Body weight is found to be a covariate affecting the exposure of R406. Exposure decreases with increasing body weight, in alignment with

allometric principles. Given a relatively high intrinsic variability in exposure among subjects due to known and unknown factors, dose adjustment by body weight alone is not warranted. Fostamatinib PK is not altered in subjects with renal impairment (creatinine clearance ≥30 to <50 mL/min), at end stage renal disease requiring dialysis or with hepatic impairment (Child-Pugh Class A, B and C).

Fostamatinib has shown to be generally safe and well-tolerated over a wide range of doses up to 600 mg. The effective concentration of R406 to inhibit Syk signaling was evaluated in a Phase 1 study with healthy subjects and in Phase 2 studies in RA patients. Results show that doses at or above 100 mg *bid* would generate effective concentrations to suppress inflammatory processes.

3.3.2 Metabolism

Fostamatinib is metabolized in the gut by alkaline phosphatase to the major active metabolite, R406. R406 is extensively metabolized, primarily through pathways of CYP450-mediated oxidation (by CYP3A4) and glucuronidation (by UDP glucuronosyltransferase [UGT]1A9). R406 is the predominant moiety in the systemic circulation, and there was minimal exposure to any R406 metabolites.

3.3.3 Drug-Drug Interactions

No significant interactions were seen with concomitant use of fostamatinib with the following drugs: methotrexate (OAT1/3 transporters), midazolam (CYP3A4 substrate), Microgynon (ethinyl estradiol and levonorgestrel), warfarin, pioglitazone (CYP2C8 substrate) and ranitidine (H2-antagonist that increases gastric pH).

3.3.3.1 Effect of Other Drugs on R406 Exposure

- A strong CYP3A4 inhibitor, ketoconazole, produced approximately 102% increase in AUC and 37% in C_{max} to R406 exposure, while a moderate inhibitor, verapamil, caused approximately 39% increase in AUC and 6% in C_{max} to R406 exposure.
- A strong inducer of multiple CYP enzymes, rifampicin, decreased exposure to R406 AUC by 75% and C_{max} by 59%.
- Single doses of rosuvastatin and simvastatin did not have a clinically relevant effect on the PK of R406.

3.3.3.2 Effect of Fostamatinib on Exposure of Other Drugs

Fostamatinib is an inhibitor of the human P-gp efflux transporter in vitro. R406 is a substrate of P-gp but not of other major transporters (OAT1/3, OCT2, OATP1B1/3, MRP2, and BCRP). R406 can inhibit CYP3A4 and BCRP and can induce CYP2C8 activity. R406 is an inhibitor of UGT1A1. Inhibition of UGT1A1 may result in increased unconjugated bilirubin in the absence of other LFT abnormalities.

- CYP3A4 substrate: Concomitant use of simvastatin (single dose 40 mg) with 100 mg twice daily fostamatinib increased simvastatin AUC by 64% and C_{max} by 113% and simvastatin acid AUC by 64% and C_{max} by 83%.

- BCRP substrate: Concomitant use of rosuvastatin (single dose 20 mg) with 100 mg twice daily fostamatinib increased rosuvastatin AUC by 95% and C_{max} by 88%.
- P-gp substrate: Concomitant use of digoxin (0.25 mg once daily) with 100 mg twice daily fostamatinib increased digoxin AUC by 37% and C_{max} by 70%.

3.4 Efficacy in wAIHA

A Phase 2 multi-center, open-label, Simon two-stage study (C788-053) in adults with AIHA who have failed at least one prior treatment regimen was conducted at sites in the US and Canada. Patients were treated for 24 weeks with fostamatinib 150 mg bid. Seventeen patients were to be enrolled initially in Stage 1. If at least 4 patients achieved a hemoglobin response (defined as hemoglobin >10 g/dL and ≥ 2 g/dL higher than baseline) by Week 24, up to 20 additional patients were to be enrolled in Stage 2 for a total of up to 37 patients. The protocol allowed up to two thirds of patients with secondary AIHA.

At the time of data cutoff for an interim analysis, a total of 19 patients with AIHA received fostamatinib in Stage 1, 17 of whom were evaluable for efficacy. Eight of the 17 patients (47%) achieved a hemoglobin response by Week 24, meeting the criteria for initiating Stage 2; a ninth subject achieved a hemoglobin response by Week 30. The extension study is ongoing. Enrollment in the Phase 2 study was halted in Aug 2018 after a decision was made to initiate a Phase 3 study in wAIHA.

3.5 Efficacy in ITP

The Phase 3 clinical program in patients with ITP was comprised of 2 completed double-blind, randomized, placebo-controlled studies (C788-047 and C788-048) and an open-label treatment extension (C788-049) in patients with persistent/chronic ITP. Studies C788-047 and C788-048 were identically designed, as randomized, double-blind, placebo-controlled, parallel group efficacy and safety studies of 24 weeks of treatment with fostamatinib compared with placebo in patients with persistent/chronic primary ITP. Randomization was in a 2:1 ratio (fostamatinib:placebo) and was stratified by baseline platelet count (<15 x 10^9/L or ≥15 x 10^9/L) and prior splenectomy (yes or no).

The initial dose was 100 mg bid, which was increased to 150 mg *bid* on or after Week 4 if platelet count was <50 x 10^9/L (and depending on tolerability).

Efficacy results from 2 Phase 3 studies and a long-term extension study demonstrate a rate of stable platelet response of 17.6%–22.7% in patients treated with fostamatinib.[8] The initial signal of a fostamatinib-associated increase in platelets was evident within 2 to 12 weeks of drug exposure. The platelet response was generally robust and durable and prompted most responders to continue on fostamatinib in the extension study. Details of the ITP studies can be found in the Investigator's Brochure.

Fostamatinib is a SYK inhibitor that was granted marketing approval by the US FDA in April 2018 for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment.

3.6 Safety

Fostamatinib has been studied in nearly 4700 subjects/patients across various populations including healthy subjects, patients with ITP, patients with RA, oncology patients, and in patients with AIHA. Details on safety information in these populations can be found in the Investigator's Brochure. Information on the most relevant populations, wAIHA and ITP, for this protocol are described below.

3.6.1 Safety in wAIHA

In Study C788-053, as of the data cutoff date of an interim analysis (08 March 2018), all 19 patients reported an AE: diarrhea was reported for 5 patients (26%); hypertension for 6 patients (32%); nausea, fatigue, insomnia and dizziness for 3 patients each (16%); ALT elevation, AST elevation, BP increased, decreased neutrophils, pyrexia, headache, upper respiratory tract infection, hypokalemia, anemia, jaundice, ocular icterus, and increased weight for 2 patients each (11%); 63% of subjects had an AE considered treatment related. The most common treatment-related AEs included diarrhea (21%), hypertension (16%), fatigue (16%), ALT/AST elevated (11%), blood pressure increased (11%), and neutrophils decreased (11%); all are consistent with the safety profile described in the ITP and RA populations.

The majority of events were mild to moderate in severity. Events of Grade-3 severity included decreased neutrophils, fatigue, skin necrosis, hypokalemia, hypophosphatemia, anemia, jaundice, contusion and prostate cancer. Of these severe events, only decreased neutrophils and fatigue were considered related to fostamatinib treatment.

The incidence of increased blood pressure was generally similar to that reported in the fostamatinib safety database; for example, out of 19 total subjects there were four subjects with normal baseline BP who developed on-treatment values as high as Stage 1 (systolic between 130–139 or diastolic between 80–89 mmHg). Regarding liver function tests, there were no cases of ALT or AST >3 x ULN. The incidence of GI-related AEs was similar to that in the fostamatinib safety database (e.g., 26% incidence of diarrhea).

Three subjects had serious adverse events (SAEs), all judged unrelated to study drug by the investigator and two of which were fatal. One subject had three SAEs of anemia, skin necrosis and fatal infection; the fatal event was a complication of the skin necrosis/possible calciphylaxis. The second subject had a fatal pneumonia considered related to underlying CLL and chronic steroid therapy. The third subject had a SAE of syndrome of inappropriate antidiuretic hormone secretion (SIADH); fostamatinib was interrupted until resolution of the event.

3.6.2 Safety in ITP

Fostamatinib was studied in 2 randomized, double-blind, placebo-controlled trials that were identical in design. The data described below reflect exposure to fostamatinib in 102 patients with persistent or chronic ITP who had received one or more prior ITP treatment(s). Groups were stratified with respect to splenectomy and severity of thrombocytopenia. Patients randomized to the fostamatinib arm received 100 mg orally *bid*. Based upon platelet count and tolerability, if a patient's platelet count did not increase to at least 50 x 10^9/L, the fostamatinib dose could be

increased to 150 mg *bid* after 1 month. In the placebo-controlled studies, the median duration of fostamatinib exposure in these studies was 86 days (range 8 to 183 days).

In the ITP double-blind studies, serious adverse drug reactions were febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis, which each occurred in 1% of patients receiving fostamatinib. In addition, severe adverse reactions observed in patients receiving fostamatinib included dyspnea and hypertension (both 2%); and neutropenia, arthralgia, chest pain, diarrhea, dizziness, nephrolithiasis, pain in extremity, toothache, syncope and hypoxia (all 1%). Table 1 presents the common adverse reactions from these studies.

Table 1: Incidence of Common (≥5%) Adverse Reactions from Double-Blind Clinical Studies (C788-047 and C788-048)

Adverse Reaction	Fostamatinib (N=102)				Placebo (N=48)			
	Mild %	Moderate %	Severe %	TOTAL %	Mild %	Moderate %	Severe %	TOTAL %
Diarrhea[a]	21	10	1	31	13	2	0	15
Hypertension[b]	17	9	2	28	10	0	2	13
Nausea	16	3	0	19	8	0	0	8
Dizziness	8	2	1	11	6	2	0	8
ALT increased	5	6	0	11	0	0	0	0
AST increased	5	4	0	9	0	0	0	0
Respiratory infection[c]	7	4	0	11	6	0	0	6
Rash[d]	8	1	0	9	2	0	0	2
Abdominal pain[e]	5	1	0	6	2	0	0	2
Fatigue	4	2	0	6	0	2	0	2
Chest pain	2	3	1	6	2	0	0	2
Neutropenia[f]	3	2	1	6	0	0	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase
Note: Common adverse reactions were defined as all adverse reactions occurring at a rate of ≥5% of patients in the fostamatinib group and greater than placebo rate.

a. Includes diarrhea and frequent bowel movement.
b. Includes hypertension, blood pressure (BP) increased, BP diastolic abnormal, and BP diastolic increased.
c. Includes upper respiratory tract infection, respiratory tract infection, lower respiratory tract infection, and viral upper respiratory tract infection.
d. Includes rash, rash erythematous, and rash macular.
e. Includes abdominal pain and abdominal pain upper.
f. Includes neutropenia and neutrophil count decreased.

Additional information from the two placebo-controlled Phase 3 ITP studies is provided for the following clinically important adverse reactions: hypertension, hepatotoxicity, diarrhea and neutropenia.

3.6.2.1 Hypertension

Increased BP, including the development of hypertension, has been reported in patients treated with fostamatinib. Hypertensive crisis occurred in 1% of ITP patients. Patients with preexisting hypertension may be more susceptible to the hypertensive effects of fostamatinib.

3.6.2.2 Hepatotoxicity

Elevated liver function test results, mainly ALT and AST, were reported in patients treated with fostamatinib. In the placebo-controlled studies, laboratory testing showed maximum ALT/AST >3 x ULN in 9% of ITP patients receiving fostamatinib and no patients receiving placebo. For most patients, transaminases recovered to baseline levels within 2 to 6 weeks of dose modification.

3.6.2.3 Diarrhea

Diarrhea occurred in 31% of ITP patients treated with fostamatinib; severe diarrhea occurred in 1% of patients treated with fostamatinib.

3.6.2.4 Neutropenia

In ITP clinical trials, neutropenia (ANC <1.0 x 10^9/L) was reported. There is no clear association between neutropenia and the risk of infection. Neutropenia occurred in 7% of patients treated with fostamatinib; febrile neutropenia occurred in 1% of patients.

3.6.3 Safety Summary

Nearly 4,700 subjects/patients have received fostamatinib as part of clinical studies in a variety of indications, including 163 patients with ITP, more than 3,400 RA patients at doses of 100 to 300 mg/day, and more than 160 oncology patients at doses of 200 to 500 mg/day; a summary of the safety profile of fostamatinib in each of these indications is provided in the Investigator's Brochure. Fostamatinib is generally well tolerated when administered at doses of 100 to 150 mg *bid*, as planned in the current study. The safety profile of fostamatinib in these studies shows a consistent pattern of adverse reactions across indications, including wAIHA and ITP as described above, with diarrhea, hypertension, nausea, and increased transaminases being the most frequent adverse reactions reported from these populations.

3.7 Potential Benefit-Risk Summary

Nonclinical data support the potential benefit of fostamatinib, a SYK inhibitor, in wAIHA. SYK plays a central role in FcRγ-bearing macrophage clearance of circulating IgG-coated RBCs, which is believed to be a pathogenic mechanism in AIHA (Section 3.1).[2] Fostamatinib administration in an animal model of wAIHA showed protection from anemia (Section 3.2).

As described in Section 3.4, an interim data cut of the open label Phase 2 study assessing fostamatinib in treatment of wAIHA patients who failed at least one prior therapy showed that 8/17 subjects (47%) in the Efficacy Evaluable Population responded during the 24-week evaluation period (lower bound of the exact 95% confidence interval is 23%); one additional subject met the response criteria in the extension period (after 24 weeks of dosing) for an overall response rate of 53% (9/17) on fostamatinib (lower bound of the exact 95% confidence interval is 31%). Thus preliminary data indicate that fostamatinib may benefit wAIHA patients who have failed at least one prior therapy.

The risks of fostamatinib have been characterized and consistent across programs including, healthy subjects, and patients with ITP, rheumatoid arthritis (RA), malignancies, IgA nephropathy and wAIHA (see Investigator's Brochure). The AEs most commonly related to fostamatinib include effects on blood pressure, hepatic transaminase elevations, gastrointestinal complaints (especially diarrhea) and neutrophil counts. These AEs are mostly mild to moderate in intensity. They are reversible and manageable with appropriate safety monitoring, medical intervention and at times fostamatinib dose reduction, interruption or discontinuation (details on Recommended Dose Modifications and Management of Specific Adverse Reactions in Appendix 2). The safety results from the Phase 2 wAIHA interim datacut (described in Section 3.6.1) are consistent with those in the entire fostamatinib safety database. SAEs in the Phase 2 wAIHA study were often related to the underlying disease or its treatment and complications. None of these SAEs were judged by investigators as related to fostamatinib.

In sum, the potential benefit of fostamatinib treatment in wAIHA patients outweighs the risks and supports the conduct of a Phase 3 study in this indication.

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

- The primary objective of this study is to compare the proportion of warm antibody autoimmune hemolytic anemia (wAIHA) subjects who achieve a durable hemoglobin response between the fostamatinib and placebo groups.

- The secondary objectives of this study are:

    1. To compare the proportion of subjects with hemoglobin response on at least one visit between the fostamatinib and placebo groups

    2. To compare the proportion of subjects who achieve a change from Baseline in hemoglobin level of ≥ 2 g/dL between the fostamatinib and placebo groups

    3. To compare the change in hemoglobin value from Baseline to the End of Treatment between the fostamatinib and placebo groups

    4. To compare the proportion of subjects who use permitted rescue medications after Week 4 between the fostamatinib and placebo groups

    5. To compare the change from Baseline to Week 24 in Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-F)

- The safety objective is to assess the safety of fostamatinib in subjects with wAIHA.

- Additional efficacy and pharmacoeconomic objectives will compare the fostamatinib and placebo groups for the following endpoints:

    - Any hemoglobin level ≥ 10 g/dL within the 24 weeks of treatment (Yes/No)

    - Any change from Baseline in hemoglobin level ≥ 1.5 g/dL within the 24 weeks of treatment (Yes/No)

    - Percentage of available visits with hemoglobin response

    - Total duration of hemoglobin response (days)

    - Total duration of hemoglobin ≥ 10 g/dL (days)

    - Time to first hemoglobin response (days)

    - Time to first rescue medication (days)

    - Net cumulative change from Baseline in corticosteroid dose (prednisone-equivalent) during the 24 weeks of treatment

- Cumulative increase from Baseline in corticosteroid dose (prednisone-equivalent) during the 24 weeks of treatment.
- Change in reticulocyte count, LDH, and haptoglobin over time
- Change from Baseline to Week 24 in EQ-5D-5L
- Change from Baseline to Week 24 in the EQ VAS
- Hospitalization related to AIHA within 24 weeks of treatment (Yes/No).
- Change from Baseline in hemoglobin level over time during the 24 weeks of treatment

4.2 Primary Efficacy Endpoint

The primary efficacy endpoint is achievement of durable hemoglobin response (Yes/No) defined as achieving a hemoglobin level ≥ 10 g/dL with an increase from Baseline in hemoglobin level of ≥ 2 g/dL on 3 consecutive available visits during the 24-week treatment period, in which hemoglobin measurements eligible for this definition occurred outside a Rescue Treatment Visit Exclusion Period (see Section 10.3.6).

4.3 Secondary Efficacy Endpoints

The secondary efficacy endpoints within the 24 weeks of treatment are:

1. Hemoglobin response on at least one visit (Yes/No)
2. Achievement of a change from Baseline in hemoglobin level of 2 g/dL or greater (Yes/No)
3. Change in hemoglobin value from Baseline to End of Treatment (Week 14 to Week 24)
4. Use of permitted rescue medications after Week 4 (Yes/No)
5. Change from Baseline to Week 24 in Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-F)

End of Treatment hemoglobin is defined as the mean of the hemoglobin values from the last 6 available visits between Week 14 and Week 24, inclusive, as long as those visits occurred outside a Rescue Treatment Visit Exclusion Period.

The FACIT-F scale is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. Each item is rated using a 5-point Likert-type scale (0 = not at all; 1 = a little bit; 2 = somewhat; 3 = quite a bit; and 4 = very much). Negatively stated items are reversed by subtracting the response from "4". After reversing proper items, all subscale items are summed to a total, which is the subscale score. All items contribute to the sum score with equal weight. The scale range is 0 to 52, with 0 being the worst possible score and 52 being the best possible score indicating no fatigue (see FACIT

Administration and Scoring Guidelines, and Cella 2002[4]). The overall score will be calculated and prorated for missing items as follows:

Total Score = [Sum of item scores] x [N of items in subscale] ÷ [N of items answered]

The FACIT-F change scores will be computed as (Week 24 score - Baseline score).

4.4 Safety Endpoints

The following safety endpoints will be evaluated:

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Incidence and severity of TEAEs of Interest
- Change from Baseline for select laboratory tests over time (e.g., hematology, chemistry)
- Change from Baseline in blood pressure over time
- Change from Baseline in absolute neutrophil count (ANC) over time
- Change from Baseline in liver function tests (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST]), total bilirubin, direct and indirect bilirubin) over time.

4.5 Additional Efficacy and Pharmacoeconomic Endpoints

The following additional efficacy and pharmacoeconomic endpoints will be evaluated:

- Any hemoglobin level ≥ 10 g/dL within the 24 weeks of treatment (Yes/No)
- Any change from Baseline in hemoglobin level ,≥1.5 g/dL within the 24 weeks of treatment (Yes/No)
- Percentage of available visits with hemoglobin response
- Total duration of hemoglobin response (days)
- Total duration of hemoglobin ≥ 10 g/dL (days)
- Time to first hemoglobin response (days)
- Time to first rescue medication (days)
- Net cumulative change from Baseline in corticosteroid dose (prednisone-equivalent) during the 24 weeks of treatment
- Cumulative increase from Baseline in corticosteroid dose (prednisone-equivalent) during the 24 weeks of treatment.

- Change in reticulocyte count, LDH, and haptoglobin over time
- Change from Baseline to Week 24 in EQ-5D-5L
- Change from Baseline to Week 24 in the EQ VAS
- Hospitalization related to AIHA within 24 weeks of treatment (Yes/No).
- Change from Baseline in hemoglobin level over time during the 24 weeks of treatment

4.6 Pharmacokinetic Endpoints

The pharmacokinetic endpoint is the plasma concentration of the active component of fostamatinib (R406) relative to the date and time of last dose of study drug, at Weeks 2, 4, 12 and 18 of the treatment period.

5.0 STUDY DESIGN

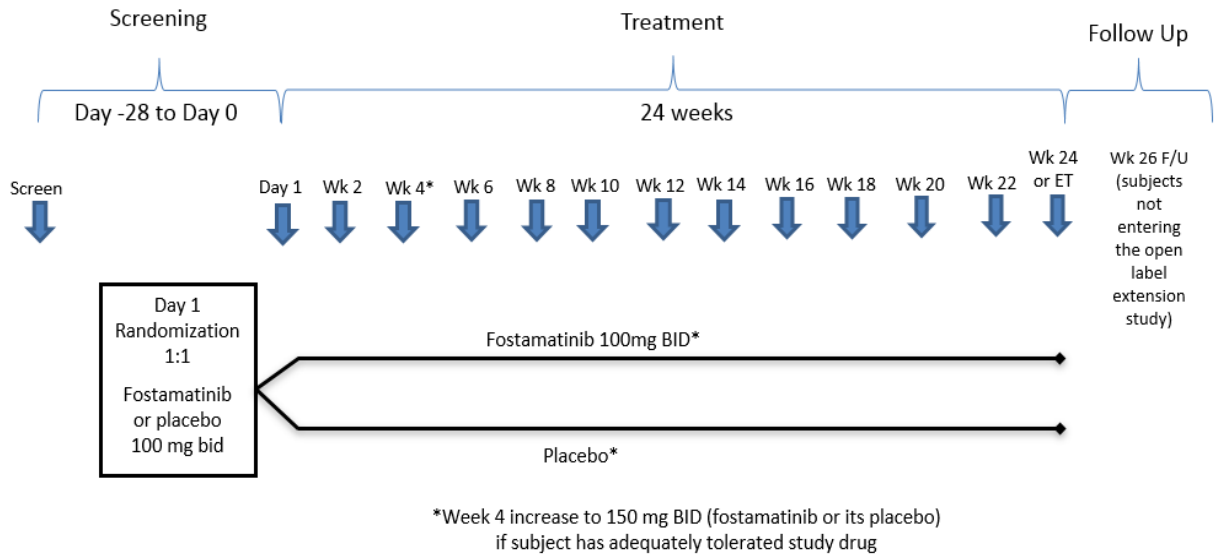
5.1 Justification of Study Design

This is a Phase 3 multicenter placebo-controlled study to evaluate the safety and efficacy of fostamatinib in patients with wAIHA. The rationale for the study comes from results from a preclinical AIHA model showing that mice treated with fostamatinib were significantly protected from anemia (see Section 3.2) as well as results from a Phase II study showing that up to 47% of patients with wAIHA achieved a hemoglobin response after treatment with fostamatinib (see Section 3.4). The basis for a randomized controlled design is to be able to distinguish the safety and efficacy results of fostamatinib as compared to the control. The choice of a placebo for the control group is justified because there is no specific treatment approved for this condition. The initial hemoglobin response was observed in the Phase II study as early as week 2 and as late as week 30. The intent of the 24-week treatment and observation period is to capture the majority of responses.

5.2 Summary of Study Description

This is a Phase 3 multi-center, randomized, double-blind, placebo-controlled, parallel group study to investigate the efficacy of 24 weeks of treatment with fostamatinib (R788) vs. placebo in achieving a durable hemoglobin response in subjects with wAIHA (Figure 2). Approximately 90 subjects will be enrolled at multiple sites. The study will consist of approximately 15 visits. The end of the study will be when the last subject has completed either the Week 24 visit or their last follow-up study visit, whichever is later.

Figure 2: Study Design



The study procedures to be performed at each visit are shown in Table 4.

Subjects will be randomized (1:1, active:placebo) to receive fostamatinib (100 mg PO *bid*) or matching placebo for 24 weeks. Randomization will be stratified by concomitant steroid use at baseline (≥20 vs. <20 mg daily) and by severity of anemia at screening (hemoglobin <9 vs. ≥9 g/dL).

5.3 Study Drug Dose Modifications

Starting at Week 4, the initial fostamatinib dose of 100 mg PO *bid* or matching placebo will be increased to fostamatinib 150 mg PO *bid* or matching placebo if subjects have adequately tolerated the study drug in the investigator's judgment.

The dose may be reduced at any time to a dose as low as fostamatinib 100 mg PO *qd* or matching placebo if dose-limiting adverse events are observed (see Dose Adjustment Table 5).

Subjects who have completed this study will be encouraged to enroll into an open-label extension study with fostamatinib. Subjects and investigators will remain blinded to the C-935788-057 treatment assignment at the time of enrollment in the extension study. Details of the dosing strategy during the open-label extension will be specified in a separate protocol.

5.4 Rationale for Proposed Dosing

The purpose of this study is to assess the efficacy of fostamatinib in patients with wAIHA who have failed at least one prior treatment regimen.

[redacted]

Phase 2 and 3 studies of fostamatinib in RA studied multiple dose levels including 50 mg PO *bid*, 100 mg PO *bid* and 150 mg PO *qd* or *bid*. Doses ranging from 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. All dose levels were generally well tolerated. The average daily R406 exposure at 150 mg PO *bid* ranged from 10,000 to 19,800 ng•h/mL. The average daily R406 exposure at 100 mg PO *bid* ranged 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 the biomarker assays described above, and support the 100 and 150 mg PO *bid* doses for this study.

In the Phase 3 ITP studies, subjects received 100 mg PO *bid* for 4 weeks; if tolerated and the platelet count had not reached a prespecified level, investigators were allowed to increase the dose to 150 mg PO bid. Both doses were effective in raising platelet counts; 76% of the patients had their fostamatinib dose increased to 150 mg PO *bid* at Week 4.

In this Phase 3 study, the starting dose will be similar to the Phase 3 ITP studies: the initial dose of fostamatinib will be 100 mg or matching placebo bid. Starting at Week 4, the initial dose will be increased to fostamatinib 150 mg PO *bid* or matching placebo *bid* (i.e., the Phase 2 AIHA dose) if subjects have adequately tolerated the study drug.

5.5 Study Drug Dose Modification

Starting at Week 4, the initial fostamatinib dose of 100 mg PO *bid* or matching placebo will be increased to fostamatinib 150 mg PO *bid* or matching placebo if subjects have adequately tolerated the study drug, in the investigator's judgment.

The dose may be reduced at any time to a dose as low as fostamatinib 100 mg PO *qd* or matching placebo if dose limiting adverse events are observed.

5.6 Study Treatment

All subjects will receive double blind treatment as indicated in Table 2.

Table 2: Double Blind Treatment

Treatment Group	Number of Subjects	Study Drug	Regimen
A	45	Placebo	*bid* (morning and evening)
B	45	Fostamatinib	*bid* (morning and evening)

5.7 Treatment Blinding and Unblinding

This is a double-blind study in which the subjects, the investigators, all other site personnel, and the Sponsor/Representative will be blinded until all subjects complete the 24 weeks of evaluation or discontinue from the study and the database is locked. At that point, Sponsor/Representative personnel will be unblinded to subject treatment assignments. Subjects, investigators, and all other site personnel will remain blinded to subject treatment assignment throughout the study. Randomization codes will be kept by the Sponsor.

At the Screening visit, each subject will be assigned a unique subject number. At the Day 1 visit, each subject will be assigned to a treatment group according to the randomization schedule. At each visit, the study drug label will indicate the study number and treatment kit number assigned by the randomization system but will not indicate the treatment assignment.

Emergency unblinding of a subject is covered in Section 8.5.

5.8 Duration of Treatment

Over the course of the study, subjects will be expected to visit the clinic approximately 15 times. Safety assessments and hemoglobin levels will be performed at each visit to evaluate the safety and efficacy of study drug (fostamatinib or placebo), and to determine if a dose adjustment is required.

5.9 Allowed AIHA Therapies

Subjects may continue concurrent steroid therapy and other wAIHA therapy (maximum of 2 therapies) as listed in Section 7.14.1.

Doses and regimens of concurrent wAIHA therapies allowed at entry may not be changed during the 24-week treatment period except for temporary steroid dose increases instituted as rescue therapy or a steroid taper as allowed by the protocol (see Section 7.9 for Rescue Protocol and Section 7.10 for Steroid Taper Protocol).

If an allowed medication is discontinued during screening, the interval between last dose of medication and randomization is per the time frames listed in Section 7.14.1.

Other medications prescribed for wAIHA, e.g. rituximab or other anti-CD20 monoclonal antibody, cyclosporine, brutinib or other BTK inhibitor, chemotherapy agents such as cyclophosphamide, vincristine, investigational agents for AIHA, etc., are not allowed during study treatment (from Day 1 until the last dose of study drug).

5.10 Randomization

A Randomization and Trial Supply Management (RTSM) system will be used to randomize subjects. The RTSM will assign a bottle of the study drug to each subject who is eligible for the double-blind treatment period of the study. An individual subject can only be randomized once for the entire study.

5.11 Safety Monitoring

The Rigel Medical Monitor and representatives will closely monitor the safety of study drug on an ongoing basis by assessing reported adverse events, vital signs, clinical laboratory values (hematology, serum chemistry, and urinalysis), and physical examinations. Refer to Section 6.6 of the Investigator's Brochure for additional guidance regarding monitoring including for infections and bone investigations.

5.12 Independent Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will also monitor safety throughout the study (Section 10.5). The rules guiding the DMC are detailed in the DMC charter.

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 undergoing any study-specific procedures.

2. Subject must have a diagnosis of primary or secondary wAIHA as documented by a positive direct antiglobulin test (DAT) specific for anti-IgG or anti-IgA. Eligibility may be based on a historical DAT obtained within 12 months of the screening visit from a local laboratory, provided that specific IgG or IgA positivity is documented; otherwise, this assay will be done at screening by a central laboratory.

3. Has failed or not tolerated at least one prior wAIHA treatment, e.g., steroids, rituximab, azathioprine, cyclophosphamide, cyclosporine, MMF, danazol, vincristine, ESA or splenectomy (folate, iron or other supplements do not fulfill this criterion).

4. Has haptoglobin <LLN **or** total bilirubin >ULN **or** lactate dehydrogenase (LDH) >ULN.

5. At screening, subject's hemoglobin level must be ≤9 g/dL

   OR

   If the hemoglobin value is >9 g/dL and <10 g/dL, subject must be on an allowed wAIHA treatment (see Allowed AIHA Therapy table) AND the subject must have documented symptoms related to anemia (e.g., weakness, dizziness, fatigue, shortness of breath, chest pain)

6. Male or female at least 18 years of age at screening.

7. Karnofsky performance status (KPS) ≥70.

8. Subject's concurrent treatment for wAIHA may consist of no more than two of any of the following agents: azathioprine, steroids, ESAs, mycophenolate mofetil, dapsone or danazol at a stable dose, as defined in the Allowed AIHA Therapies table. Subject has not taken any disallowed therapies in the intervals defined by the protocol.

9. Female subjects must be either post-menopausal for at least 1 year or surgically sterile; or, if of childbearing potential, must not be pregnant or lactating and must agree to use a highly effective 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 screening, an intrauterine device (IUD), or intrauterine hormone-releasing system (IUS), or true abstinence (i.e. abstinence is in line with the preferred and usual lifestyle of the subject).

10. 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. Subject with other types of AIHA (e.g., cold antibody AIHA, cold agglutinin syndrome, mixed type AIHA, or paroxysmal cold hemoglobinuria).

2. Subject has AIHA secondary to autoimmune disease, including systemic lupus erythematosus (SLE), or lymphoid malignancy if the underlying disease is not stable or is not well-controlled on current therapy, per investigator medical judgment.

3. Subject has a history of or active, clinically significant, cardiovascular, respiratory, gastrointestinal, renal, hepatic, neurological, psychiatric, musculoskeletal, genitourinary, dermatological, or other disorder that, in the investigator's opinion, could affect the conduct of the study or the absorption, metabolism or excretion of the study drug.

4. Subject has uncontrolled or poorly controlled hypertension, defined as systolic blood pressure ≥135 mmHg or diastolic blood pressure ≥85 mmHg, whether or not the subject is receiving anti-hypertensive treatment.

5. Subject has one or more of the following laboratory abnormalities at screening: neutrophil count of <1,000/µL or platelet count of <30,000/µL, unless due to Evans syndrome; transaminase levels (i.e., alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) >1.5 x ULN.

6. Has documented HIV infection or active hepatitis B or hepatitis C infection.

7. Subject is currently enrolled in an investigational drug or device study or has used an investigational drug or device within 30 days or 5 half-lives (whichever is longer) of Day 1.

8. In the judgment of the investigator, the subject may not be able to fully comply with study requirements.

9. Subject has been treated with fostamatinib previously for any indication.

10. Subject has a known allergy and/or sensitivity to the test article or its components.

11. Subject has had a splenectomy within the past 4 weeks.

Exemptions or exceptions to the inclusion or exclusion criteria are not allowed.

6.3 Disallowed AIHA Therapies

Disallowed AIHA Therapies: Any of the disallowed therapies below in Table 3 may not be taken within the indicated interval prior to Day 1.

Table 3: Disallowed AIHA Therapies Requirements

Drug	**Prohibited Period Prior to Day 1** (from last dose of agent)
RBC transfusion	7 days
IVIg	14 days
Cyclosporine	30 days
Rituximab or other anti-CD20 monoclonal antibody	8 weeks
Ibrutinib or other BTK inhibitor	4 weeks
Chemotherapy agents (e.g., cyclophosphamide, vincristine)	6 weeks
Investigational agent	30 days or 5 half-lives, whichever is greater

7.0 STUDY PROCEDURES

The study procedures to be performed at each visit are shown in Table 4.

Table 4: Schedule of Procedures

Study Procedure	Screening	Baseline	Weeks (allowed visit windows ±3 days)												Follow- Up [g]
	Day -28 to Day -1	Day 1 Wk 0	Wk 2	Wk 4 [f]	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24/ Early Term	Wk 26 ± 3 days
Informed Consent	X														
Inclusion/Exclusion	X														
Demographics [a]	X														
Medical History	X	X													
Physical Exam	X													X	
Abbreviated Physical Exam		X	X	X	X	X	X	X	X	X	X	X	X		X
Adverse Events [b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X														
Weight	X							X						X	
KPS	X													X	
FACIT and EQ-5D[c]		X						X						X	
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG	X														
Reticulocyte Count		X				X				X				X	X
Haptoglobin	X	X				X				X				X	X
DAT specific for anti-IgG or IgA [e]	X														
Complete Blood Count with Differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Chemistry with LFTs	X	X				X				X				X	X
LFTs				X				X				X	X		
Plasma for PK Samples			X	X				X			X				
Urinalysis	X	X				X				X				X	X
Serum Pregnancy Test [h]	X	X		X		X		X		X		X		X	X
Study Drug Dispensed		X		X		X		X		X		X			
Study Drug Accountability				X		X		X		X		X		X	

a. Demographics include sex, race/ethnicity and age.
b. Adverse Events – Reporting period begins when the consent is signed.
c. FACIT and EQ-5D – subject is to read questionnaire by him/herself and write/mark answers directly onto the questionnaire. When possible, administer the questionnaires at the start of the visit. Site staff to check only for completeness of each questionnaire.
d. Vital Signs include blood pressure, pulse and temperature. All blood pressure determinations should be made with the subject seated and taken after the subject rests for 5 minutes. If the initial blood pressure at any visit, is ≥130 mmHg systolic or ≥ 80 mmHg diastolic (≥135 or ≥85 at screening), the subject should remain seated and blood pressure should be taken 2 additional times at least 3 minutes apart. If the average of the 3 BP measurements is ≥130 mmHg systolic or ≥80 mmHg diastolic, follow the dose modification recommendations in Appendix 2.
e. Screening DAT - Eligibility may be based on a historical DAT obtained within 12 months of the screening visit from a local lab provided that specific IgG or IgA positivity is documented, or this assay will be done at screening at a central laboratory.
f. At Week 4, the dose of study drug will be increased to 150mg *bid* if the subject has adequately tolerated the study drug, based on the investigator's judgment.
g. Follow-up Visit performed ONLY on subjects not entering the Open Label Study.
h. Serum pregnancy test only for women of child bearing potential.

7.1 Screening

7.1.1 Screening Visit (Day -28 to -1)

Subjects must be willing to sign and date an Institutional Review Board (IRB)-approved informed consent form (ICF) prior to participating in any study-specific screening procedure activities.

Screening evaluations will be used to determine the eligibility of each subject prior to initiation of treatment.

Screening assessments may be repeated up to two additional times during the 28-day screening window. This restriction does not apply to instances where the result was not obtained such as a hemolyzed laboratory sample.

Subjects who fail to meet eligibility criteria or have screening assessments performed outside of 28 days of randomization should be rescreened.

Subjects who fail to meet eligibility criteria may be re-screened up to two times if there is a reasonable expectation that the subject will be eligible after the repeat screen(s) (for example, following successful treatment of hypertension).

Sites will be required to complete and send an eligibility verification form to the Medical Monitor for review and approval prior to randomizing a subject.

The following assessments will be completed as part of the screening visit (up to 28 days prior to Baseline/Day 1):

- Inclusion/Exclusion Criteria
- Demographics: sex, race/ethnicity and age
- Medical and wAIHA treatment history
- Physical examination and KPS
- Height and weight
- Prior and Concomitant Medications (30 days prior to baseline for prior non-AIHA meds; all prior AIHA therapies prior to baseline)
- Vital Signs, including blood pressure, should be taken with the subject seated and after the subject rests for 5 minutes. If the blood pressure is outside the parameters for inclusion (≥135 mmHg systolic, or diastolic blood pressure ≥85 mmHg), the subject should remain seated and the measurement should be taken 2 more times at least 3 minutes apart. The average of these 3 measurements will be used to determine eligibility.
- 12-Lead ECG

- DAT (results must be positive for anti-IgG or IgA; historical results are acceptable within 12 months of screening from a local laboratory; otherwise testing will be done centrally).
- Complete Blood Count (CBC) with differential
- Serum Chemistry (with LFTs)
- Haptoglobin
- Urinalysis
- Serum Pregnancy Test (for females of childbearing potential)

7.2 Baseline/Day 1/First Dose (Day 1/Week 0)

The Baseline/First Dose visit will occur within 28 days after screening.

To be eligible for enrollment in the study, subjects must have met all inclusion/exclusion criteria at the baseline visit prior to first dose.

The Medical Monitor must review and approve each subject's eligibility verification form prior to randomization.

The following assessments will be completed prior to study drug administration:

- Changes in medical history
- FACIT-F and EQ-5D Questionnaires: Subject is to read questionnaire by him/herself and write/mark answers directly onto the questionnaire
- Abbreviated physical examination
- Concomitant Medications
- Vital Signs (blood pressure[1], pulse, and temperature)
- Hemoglobin level and reticulocyte count
- CBC, differential, and platelet count
- Serum Chemistry (with LFTs)
- Haptoglobin
- [redacted] (see Section 7.13.7)

[1] NOTE: If the initial blood pressure at any visit is ≥130 mmHg systolic or ≥80 mmHg diastolic, the subject should remain seated and the blood pressure should be taken at least 2 additional times at least 3 minutes apart. If the average of the 3 measurements is ≥130 mmHg systolic or ≥80 mmHg diastolic, follow the guidelines in Appendix 2.

- Urinalysis
- Serum pregnancy test (for females of childbearing potential)
- Randomize for drug assignment in RTSM system

All subjects start the study at the 100mg dose. The first dose of study drug should be administered in the clinic to ensure that the subject understands dosing instructions. For all subjects, this dose will be considered the evening dose for this day no matter what time it is administered. Study staff will instruct the subject to take the study drug *bid* beginning the following morning. See Section 8.4 for additional information regarding study drug dispensation and administration.

7.3 Treatment Period Visits, Weeks 2-24

The treatment period begins at baseline (Day 1) and continues for a total of 24 weeks. All subsequent visits are determined by the date of the baseline visit and should occur within the visit windows specified in Table 4. Over the course of the study subjects will be expected to visit the clinic approximately 15 times. Safety assessments and hemoglobin levels will be performed at each visit to evaluate the safety and efficacy of fostamatinib and to determine if a dose adjustment is required. At Week 24 subjects who do not agree to participation in the open label extension study will complete the Week 24 visit and return two weeks later for a follow up visit.

Starting at Week 4, the initial fostamatinib dose of 100 mg PO *bid* or matching placebo will be increased to fostamatinib 150 mg PO *bid* or matching placebo if subjects have adequately tolerated the study drug, based on the investigator's judgment.

Subjects who agree to participate in the open label extension study will complete the Week 24 visit and follow the enrollment procedures for the open label extension study, as noted in the extension study protocol.

Refer to Table 4 for the complete schedule of study procedures.

Refer to Appendix 7 for guidance in the event of a pandemic for screening and on study visits.

7.4 Unscheduled Visits

Subject visits conducted outside of the scheduled protocol visits should be captured in the subject's medical record and CRF.

7.5 Study Follow-Up (Week 26 or 2 weeks after Early Termination/Discontinuation)

Subjects who choose not to continue on to the open label study or who have discontinued or terminated the study will return two weeks following the last dose of study drug for follow-up study assessments.

If an SAE is present at the visit, follow-up should occur as indicated in Section 9.2.1.

7.6 Withdrawal from Study

Study medication may be discontinued and the subject withdrawn in the following instances:

- Intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree;
- Unacceptable toxicity, as defined in the toxicity management section of the protocol, or toxicity that, in the judgment of the investigator, compromises the ability to continue study-specific procedures or is considered to not be in the subject's best interest;
- Subjects requiring any AIHA therapies other than those allowed or requiring an escalation of the allowed concurrent medications other than steroids
- Subject request to discontinue for any reason;
- Subject noncompliance;
- Pregnancy during the study; or
- Discontinuation of the study or subject at the request of Rigel, a regulatory agency or an IRB.

Subjects who withdraw early from the study will have follow up study assessments approximately two weeks after the last dose of study drug, similar to the Week 26 assessments. The reason for withdrawal must be noted. 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 9.2.1.

7.7 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.
- The investigator becomes aware of any circumstances during the study that may reasonably indicate that the study should be terminated. In this case, 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.
- Failure by the investigational site to adhere to protocol requirements.

7.8 Dose Adjustments

7.8.1 Dose Escalation Beginning at Week 4

The initial dose of fostamatinib will be 100 mg PO *bid* or matching placebo.

Starting at Week 4, the initial fostamatinib dose of 100 mg PO *bid* or matching placebo will be increased to fostamatinib 150 mg PO *bid* or matching placebo if subjects have adequately tolerated the study drug in the investigator's judgment.

7.8.2 Dose Adjustments Due to Adverse Events

Clinical testing to date has identified adverse events 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 (see Appendix 2 for guidance regarding AE-related dose adjustments):

- Increases in ALT or AST;
- ANC <1000 / mm^3;
- Severe diarrhea;
- Hypertension; or
- Severe or life-threatening adverse events considered to be 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 the required the dose reduction, 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*.

Subjects whose dose reduction results in a once daily dose of fostamatinib will take the daily study drug dose in the morning. Table 5 details the strategy for dose adjustment in subjects who experience AEs requiring dose reduction. Appendix 2 provides the recommended dose modifications for specific adverse events.

Table 5: Dose Adjustment

Starting Dose	Dose Level -1	Dose Level -2	Dose Level -3	Dose Level -4
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

7.9 Rescue Protocol

Use of rescue medications including increases in steroid doses should be avoided for the duration of the study unless medically necessary. Rescue may be given following a decrease in Hgb of >1.5 g/dL from baseline **OR** new or worsening symptoms of anemia, so long as urgent treatment is required in the judgment of the Investigator. In subjects meeting these criteria, the following rescue regimens are permitted:

1. Increase or initiate steroid dose up to 80 mg/daily prednisone (or equivalent) for approximately 2 weeks or until clinically stable, then taper the dose by 10 to 20 mg prednisone (or equivalent) per week until return to baseline dose level (see Appendix 3 for prednisone equivalents conversion table);

2. IV methylprednisolone up to 1 g/day x 1 day up to 3 days;

3. Oral dexamethasone up to 40 mg/day x up to 4 days;

4. Red blood cell (RBC) transfusion;

5. IVIg: up to 1g/kg x 1 day up to 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. The use of any rescue therapy regimen not noted above is not permitted. Only the rescue regimens above are allowed.

7.10 Steroid Taper Protocol:

For subjects who have reached Week 12, achieved a durable response and have had at least 2 subsequent *scheduled* visits with hemoglobin assessments showing continued response, a steroid taper may be considered as follows:

- If the dose is above 20 mg/day prednisone (or equivalent), decrease dose level by 10 mg* (or equivalent) every other week, until the dose level is 20 mg/day prednisone (or equivalent). Then decrease the dose by 5 mg increments every other week until the dose is 10 mg/day and maintain. See Appendix 3 for prednisone equivalents conversion table.

- The taper may be suspended at any dose level to maintain the hemoglobin response and as needed for subject safety (e.g., to avoid adrenal insufficiency).

- If a decrease in hemoglobin of ≥0.5 g/dL is observed at any subsequent visit (as compared to either the last hemoglobin obtained prior to initiating the taper OR the previous hemoglobin assessment), the current steroid dose level should be maintained and the hemoglobin repeated in 3 days to assure no recurrence of hemolysis. A sustained (at least 2 consecutive hemoglobin results) decrease in hemoglobin of ≥1.0 g/dL should prompt a re-escalation of prednisone (or equivalent) dose to the previous, higher dose level.

- If the steroid dose is 10 mg/day prednisone (or equivalent) or below, no steroid tapering is allowed in this study.

*If the steroid dose is 25 mg/day of prednisone or equivalent, decrease the dose by 5 mg increments to 10 mg/day and maintain. For example, if the dose is 35 mg/day of prednisone or equivalent (or higher dose that is a multiple of 5), decrease the dose in 10 mg increments as described above to 25 mg/day for 2 weeks; then decrease in 5 mg increments to 10 mg/day and maintain.

Consideration of a steroid taper is to be discussed with the Medical Monitor prior to initiating any changes.

7.11 Concomitant Erythropoietin Stimulating Agents

In subjects meeting the above response criteria (durable response and 2 subsequent scheduled visits with hemoglobin showing continued response); if the hemoglobin increases to above the upper limit of normal the ESA dose may be reduced by 50% every 4 weeks.

7.12 Missed Doses/Dose Interruptions

Missed doses will be considered as a dose interruption if the prescribed doses have been missed for two or more consecutive days.

Restarting study drug after interruption may require performance of procedures for safety that were missed during the interruption. The Medical Monitor should be consulted when considering study drug restart after a prolonged interruption (e.g., > 2 weeks).

7.13 Definition of Study Procedures

7.13.1 Medical History

The following documentation will be collected at screening and reviewed at baseline (Day 1):

- Medical/surgical history
- The date/year of AIHA diagnosis
- All previous treatments for AIHA
- Active AIHA treatment

7.13.1.1 Physical Exam

A complete physical exam will be done at screening and Week 24/ET and should include evaluation of the head, eyes, ears, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems as well as an assessment of KPS. Height and weight will be collected at screening. Weight will be collected again at Week 12 and Week 24/ET. Abbreviated physical examinations will be performed as per the study

schedule in Table 4. Prior to initiation of treatment, any new or worsened abnormalities should be recorded as medical history. Following the initiation of study treatment, any clinically significant new or worsened abnormalities will be recorded as adverse events.

7.13.1.2 Karnofsky Performance Status Assessment

The KPS (see Appendix 1) is a widely used method of assessing the functional status of patients.[9] KPS score 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).

7.13.1.3 Vital Signs

Vital signs (blood pressure, pulse, and temperature) will be assessed at all study visits. All blood pressure determinations should be made with the subject seated and taken after the subject rests for 5 minutes.

If the initial blood pressure at any visit other than screening is ≥130 mmHg systolic or ≥80 mmHg diastolic, the subject should remain seated and the blood pressure should be taken 2 additional times at least 3 minutes apart. If the average of the 3 measurements is ≥130 mmHg systolic or diastolic is ≥80 mmHg, follow the guidelines in Appendix 2.

7.13.2 Questionnaires

The FACIT-F and EQ-5D-5L subjects' reported outcomes (PRO) will be administered at Baseline, Week 12 and Week 24 (Early Termination). The subject is to read questionnaire by him/herself and write/mark answers directly onto the questionnaire. Questionnaires should be checked for completeness only.

7.13.3 Electrocardiogram

A 12-lead ECG will be obtained after 5 minutes of rest in the supine position using equipment at the site at screening. The Investigator or designee will evaluate the ECG for abnormalities.

7.13.4 Laboratory Tests

Laboratory samples will be collected, processed, shipped and managed according to the lab manual. Samples will be obtained at each study visit according to the schedule in Table 4. The total amount of blood collected for the duration of the 24-week study and 28-day screening period study is approximately 200 mL.

The following tests are to be collected and analyzed for the study:

- DAT specific for anti-IgG. Eligibility may be based on a historical DAT obtained within 12 months of the screening visit from a local laboratory, provided that specific IgG positivity is documented; otherwise, this assay will be done at screening by a central laboratory;

- Haptoglobin;
- Hematology: hemoglobin; red blood cell count (RBC); white blood cell count (WBC), platelet count, hematocrit, WBC differential count (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean platelet volume (MPV), and red blood cell distribution width (RDW);
- Serum Chemistry: includes Na, K, Cl, bicarbonate (CO_2), Ca, PO_4, blood urea nitrogen (BUN), creatinine, globulin, random glucose, LDH, AST, ALT, alkaline phosphatase, total bilirubin, direct and indirect bilirubin, total protein, albumin;
- Reticulocyte count;
- Liver Function Tests: includes ALT, AST, alkaline phosphatase, LDH, total, direct and indirect bilirubin; and
- Urinalysis (UA): appearance, glucose, ketones, blood, protein, nitrate, bilirubin, specific gravity, pH, urobilinogen, and leukocytes. A microscopic urinalysis will be performed if protein, leukocyte esterase, blood, or nitrite are abnormal.

An abnormal laboratory value is clinically significant if it meets any of the following criteria, and as such should be documented on the AE page of the eCRF:

- Test result is associated with accompanying symptom;
- Test result requires additional diagnostic testing or medical/surgical intervention;
- Test result leads to change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; or
- Test result is considered an AE by the Investigator or Sponsor.

Any laboratory result abnormality fulfilling the criteria for an SAE should be reported as such, in addition to being recorded as an AE.

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(s), is identified.

7.13.5 Pregnancy Tests

Serum pregnancy tests will be performed by the central laboratory for all female subjects of childbearing potential at the screening and baseline visits and then monthly during 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).

7.13.6 Pharmacokinetic Samples

Plasma will be collected according to the schedule in Table 4 for PK analysis. PK will be drawn at the Week 2, 4, 12, and 18 visits. The timing of the PK sampling as well as the date and time of the last dose of study drug will be recorded. Subjects are not required to take study drug in the clinic the day the sample is collected. 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 further metabolite identification and/or evaluation of the bio-analytical method in relation to this study. Data from these analyses will be used by Rigel for internal research purposes related to this study and will not be included in the clinical report. All samples will be destroyed after analysis or expiration of the 5-year time period.

7.13.7 [redacted]

[redacted]

[redacted]

7.14 Concomitant, Allowed and Restricted Therapies

Concomitant therapies will be recorded in the eCRF at the Screening Visit (for all concomitant therapies 30 days prior to baseline) through Week 24.

7.14.1 Allowed AIHA Therapies

Subjects may continue concurrent steroid therapy and other wAIHA therapy (maximum of 2 therapies) as listed below throughout their participation in the study (note: throughout this document the term ‘steroid’ indicates corticosteroid drugs as well as glucocorticoids). If an allowed medication is discontinued during screening, the interval between last dose of medication and randomization must meet the time frames listed in the table below:

Medication	Number of weeks required to be at stable dose prior to randomization	Minimum required interval between discontinuation and randomization
Azathioprine	4 weeks	4 weeks
Steroids, including dexamethasone	2 weeks	2 weeks
Erythropoiesis-stimulating agents	4 weeks	4 weeks
Mycophenolate Mofetil	4 weeks	4 weeks
Dapsone	4 weeks	4 weeks
Danazol	4 weeks	4 weeks

Doses and regimens of concurrent wAIHA therapies allowed at entry may not be changed during the 24-week treatment period except for temporary steroid dose increases instituted as rescue therapy or a steroid taper as allowed by the protocol (see Section 7.9 for Rescue Protocol and Section 7.10 for Steroid Taper Protocol).

If Promacta is being given as a concurrent medication, the dose must be stable for 4 weeks prior to randomization.

Splenectomy and other medications when prescribed for wAIHA (e.g., rituximab or other anti-CD20 monoclonal antibody, cyclosporine, ibrutinib or other BTK inhibitor, chemotherapy agents such as cyclophosphamide, vincristine, investigational agents for AIHA, etc.) are not allowed during study treatment (from Day 1 until the last dose of study drug). Subjects requiring any AIHA therapies other than those allowed, or an escalation of the allowed medications other than steroids should be withdrawn from the study. The Medical Monitor should be consulted in these instances.

7.14.2 Restricted Medications Unrelated to AIHA

Due to the potential for drug-drug interactions with fostamatinib, the following specific treatments are either not allowed or restricted during the course of the study.

7.14.2.1 Effect of Other Drugs on Fostamatinib

Drug	Restriction
CYP3A4 inhibitors and inducers	Concomitant use with strong CYP3A4 inhibitors increases exposure to R406 (the major active metabolite), which may increase the risk of adverse reactions. Monitor for toxicities of fostamatinib that may require dose reduction when given concurrently with a strong CYP3A4 inhibitor. Concomitant use with a strong CYP3A4 inducer reduces exposure to R406. Concomitant use of fostamatinib with strong CYP3A4 inducers is not recommended.

7.14.2.2 Effect of Fostamatinib on Other Drugs

CYP3A4 substrates	Concomitant use of fostamatinib may increase concentrations of some CYP3A4 substrate drugs. Monitor for toxicities of CYP3A4 substrate drug that may require dosage reduction when given concurrently with fostamatinib.
BCRP substrates	Concomitant use of fostamatinib may increase concentrations of BCRP substrate drugs (e.g., rosuvastatin). Monitor for toxicities of BCRP substrate drug that may require dosage reduction when given concurrently with fostamatinib.
P-Glycoprotein (P-gp) substrates	Concomitant use of fostamatinib may increase concentrations of P-gp substrates (e.g., digoxin). Monitor for toxicities of the P-gp substrate drug that may require dosage reduction when given concurrently with fostamatinib.

Subjects' concomitant medications should be examined for additional possible drug-drug interactions.

A list of Inhibitors and Inducers of CYP3A4 can be found in Appendix 4.

8.0 STUDY DRUG

8.1 Study Drug Description

Fostamatinib and matching placebo are supplied as orange film coated tablets in 2 dosage strengths: 100 mg and 150 mg. Each bottle of study drug contains 60 tablets. Study drug will be labeled in accordance with Current Good Manufacturing Practices (cGMP)s, 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. Each tablet contains 100 mg of fostamatinib and the inactive ingredients of the tablet core are mannitol, sodium bicarbonate, sodium starch glycolate, povidone, magnesium stearate. The inactive ingredients of the film coating are polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide (yellow), and iron oxide (red).

Matching placebo tablets containing magnesium stearate, microcrystalline cellulose and lactose monohydrate. The inactive ingredients of the film coating are polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide (yellow), and iron oxide (red) are supplied.

8.1.2 150 mg Tablets

Fostamatinib 150 mg tablets are supplied as orange film coated, plain, oval, biconvex tablets. Each tablet contains 150 mg of fostamatinib and the inactive ingredients of the tablet core are mannitol, sodium bicarbonate, sodium starch glycolate, povidone, magnesium stearate. The inactive ingredients of the film coating are polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide (yellow), and iron oxide (red).

Matching placebo tablets containing magnesium stearate, microcrystalline cellulose and lactose monohydrate. The inactive ingredients of the film coating are polyvinyl alcohol, titanium dioxide, polyethylene glycol 3350, talc, iron oxide (yellow), and iron oxide (red) are supplied.

8.2 Storage

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

8.3 How Supplied/Study Drug Dispensation

Fostamatinib and matching placebo are supplied in white opaque HDPE bottles capped with white polypropylene child resistant closures with foil induction seals.

- At Week 0/Baseline, subjects will be randomized via the RTSM system. Two bottles of assigned study drug should be dispensed. The first dose of study drug should be administered in the clinic to ensure that the subject understands dosing instructions
- At the monthly visits (Weeks 4, 8, 12, 16, 20), subjects will be instructed to bring any open bottles containing any unused study drug for accountability. Study drug will be

dispensed to cover dosing until the next visit. Subjects may keep a back up bottle for the duration of the study or until the dose is changed.

- In the event a subject loses a bottle or does not have enough study drug to last until the next monthly visit, one extra bottle of study medication may be dispensed.
- At Week 24, the final bottles dispensed will be collected and reviewed for drug accountability. Any remaining bottles previously dispensed to the subject and not previously collected (such as those dispensed at unscheduled visits or for dose modifications) will be collected for final drug accountability.

Eligible subjects enrolling in the open label extension study will be dispensed a separate supply not used in this study via the RTSM system.

8.4 Study Drug Administration

For bid dosing, subjects will self-administer one tablet twice daily by mouth: once in the morning and once in the evening, at least 8 hours apart. For *qd* dosing, subjects will self-administer one tablet daily by mouth in the morning. Subjects should be instructed that, if they miss a dose, they should take the next dose at the normal time and should not take two doses at the same time to make up for the missed dose.

Tablets may be taken with or without food. In the event of gastric upset, it may be useful to take tablets with food.

8.5 Emergency Unblinding

In the event of a medical emergency, when management of a subject's condition requires knowledge of the study drug, the subject's treatment assignment may be unblinded to disclose the identity of the study drug dispensed. Investigators will utilize the RTSM if unblinding is considered warranted. The RTSM will record the reason for unblinding, the name of the user account that performed the unblinding, and the date and time of the unblinding on the unblinding confirmation. Unblinding should only be performed if it will affect the way the subject would be treated.

8.6 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 of study drug inventory and dispensation must be maintained. All records must be made available to the Sponsor (or designee) and appropriate regulatory agencies upon request.

Study drug is manufactured, packaged and labelled in accordance with the principles and guidelines of cGMPs (Directive 2003/94/EC). Treatment compliance will be monitored via study documentation including patient records and drug accountability logs.

The study Pharmacy Manual provides detailed instructions regarding the preparation and handling of study drug.

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.[10, 11]

Changes in hemoglobin that meet the study criteria for clinical significance (protocol Section 7.13.4) should be captured as adverse events.

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;

- 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; and

- Complications that occur as a result of protocol-mandated interventions such as a venipuncture.

The following are generally NOT considered an AE:

- Pre-Existing Condition: A pre-existing condition (documented on the medical history eCRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period; or

- 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.

Assessment of Severity: Refer to CTCAE criteria version 5.0 November 27, 2017 as guidance for grading of adverse events. If the event is not listed within CTCAE categories or judged as CTCAE greater than Grade 3, then the intensity of an event should be evaluated as referred to below:

- Grade 1 (Mild) – asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2 (Moderate) – minimal, local or noninvasive intervention indicated;

- Grade 3 (Severe) – severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; age-appropriate, instrumental activities of daily life are limited.

- Grade 4 – Life threatening consequences; urgent intervention indicated; self-care activities of daily life are limited.

- Grade 5 – Death related to AE.

Serious Adverse Event (SAE):

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.

A serious adverse event (experience) 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 (e.g., the AE results in substantial disruption of the subject's ability to conduct normal life functions); or

- Is a congenital anomaly/birth defect;

- Is considered an important medical event (or medically significant) that may not result in any of the above outcomes but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed

Medical and scientific judgment should be exercised in deciding whether other situations, such as important medical events, should also be considered serious. Some 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 medically significant, the event will be considered as such or an important medical event in the absence of other seriousness criteria.

The following hospitalizations are NOT considered an SAE:

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 initiation of treatment in the study will not be considered as SAEs if they are performed after initiation of treatment in the study for a condition that has not changed from its baseline level. Hospitalizations for social or administrative reasons, due to long travel distances, or emergency room admissions of less than 24 hours are also not considered SAEs.

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 (e.g., 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 (e.g., 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 (e.g., strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive; but often, more than 1 occurrence (from 1 or multiple studies) would be needed before the Sponsor could make a determination of whether the study drug caused the event; or

- 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 (e.g., 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 (e.g., 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 are 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 will be regarded as "unexpected". 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 (e.g., whether there is a reasonable possibility that the study drug caused the event) using the following definitions:

- **Definitely Related**: A reaction that has reasonable evidence showing a direct causal relationship;
- **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; and
- **Not Related**: A reaction that does not have any reasonable suspected causal relationship.

If the relationship of an adverse event to study drug is determined to be definitely related, probable, or possible, then the relationship assigned for the purposes of regulatory reporting will be "yes."

If the relationship of an adverse event to study drug is determined to be unlikely or not related, then the relationship assigned for the purposes of regulatory reporting will be "no."

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 with the exception of screen failures. The Investigator is not required to record screen failure AE/SAEs on the eCRF. These are recorded on an SAE Form and submitted to Drug Safety only per the expedited reporting process for SAEs (see Section 9.2.3).

9.2.1 Adverse Event Reporting Period

The AE reporting period begins with the signing of the initial informed consent form (or the first informed consent form if more than one informed consent is signed due to rescreening) and ends with the final study (follow-up) visit.

If an AE or SAE is present at the withdrawal visit or at the subject's last participation in the study, it should be followed until time of resolution or stabilized unless the subjects 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.

Any SAE occurring within 14 days of the last dose of study drug should be reported.

In case of ongoing SAEs at the time of database closure, the data obtained at the time 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 (e.g., 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 the Medical Monitor 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: +1.650.745.0971

The site may contact Rigel Drug Safety at the above fax/e-mail with questions regarding reporting of SAEs.

Reporting of SUSARs will be in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

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 (e.g., 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.

For the purposes of expedited regulatory reporting, only those SAEs that are assessed as Suspected Adverse Reactions and unexpected per the Investigator's Brochure will be unblinded by a Rigel Safety representative or designee. All other study personnel, including clinical sites and investigators shall remain blinded to the unblinded subject's treatment assignment.

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 (e.g., 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 initial notification and outcome of any pregnancy that occurs during the study must be documented. The pregnancy in a female study participant and the pregnancy outcome must be reported to Rigel Drug Safety within 24 hours of awareness as outlined in Section 9.2.3, using an SAE form and the applicable pregnancy form (i.e. Exposure in Utero Form – Part I or Exposure in Utero Follow-up Form – Part II). Partners that become pregnant by a male subject do not need to report pregnancy.

Prior to screening, 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 24 hours 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 24 hours of investigator's first knowledge of such information using the pregnancy exposure form.

9.5 Special Situation Events

Other events that may or may not be associated with an AE/SAE or regarded as such are considered "Special Situation Events" and are reportable to Rigel Drug Safety within 24 hours of awareness. These are events of medication error, overdose, misuse, abuse, or inadvertent or accidental drug exposure.

- Medication error: an unintentional error in the prescribing, dispensing, or administration of the study drug
- Overdose: there is an AE associated with the overdose OR the dose or dosage regimen administered significantly exceeds the weekly prescribed dose in the judgment of the medical monitor.
- Misuse: intentional and inappropriate use of study drug not in accordance with study drug administration instructions
- Abuse: intentional and excessive use of study drug, either persistent or sporadic
- Inadvertent or accidental exposure: unintended exposure to study drug that may result in noxious and/or harmful consequences to the person who is exposed

In addition, the Investigator should notify the Medical Monitor if a subject meets Hy's Law criteria 1 and 2 to confirm whether an event meets all three of the criteria for Hy's Law, as shown below:

1. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN).
2. Total bilirubin (total BL) >2x ULN and alkaline phosphatase (ALP) <2x ULN.
3. No other reason can be found to explain the combination of increased ALT and total BL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury.

Any confirmed cases of Hy's law should be reported per the requirements in Section 9.2.3.

10.0 DATA ANALYSIS AND STATISTICAL METHODS

This section provides the key details of the statistical analyses to be performed using data captured according to this protocol. A complete statistical analysis plan (SAP) describing all planned analyses will be finalized prior to database lock.

10.1 Determination of Sample Size

The sample size is based on the number of subjects necessary to demonstrate efficacy in the primary endpoint: achievement of durable hemoglobin response (Yes/No).

Sample Size for Primary Endpoint: Achievement of durable hemoglobin response

In a previous phase 2 study, the efficacy of 12 to 24 weeks of treatment with fostamatinib in subjects with wAIHA who had failed at least one prior treatment regimen was evaluated. Approximately 27% (7 out of 26) of subjects treated with fostamatinib achieved a durable response, defined as a hemoglobin level above 10 g/dL with at least 2 g/dL higher than the baseline hemoglobin, not attributable to RBC transfusion or other rescue treatments on at least 3 scheduled visits within 24 weeks of treatment. No data are available on placebo response rates for this population. It is expected that no more than approximately 5% of placebo subjects would achieve a durable hemoglobin response.

Under these assumptions, a sample size of 90 subjects (i.e., 45 subjects per treatment group) will yield at least 84% power to detect a difference between the 2 groups at the 0.05 two-sided significance level using Fisher's exact test.

10.2 Analysis Populations

The following populations will be considered for analysis of various endpoints:

- *Intent-to-Treat Population (ITT)*: Includes all randomized subjects according to the randomized treatment assignment.

- *Per-Protocol Population (PP)*: Include all subjects in the ITT population without major protocol deviations which may affect the evaluation of the primary efficacy endpoints. For analysis purposes, subjects will be grouped according to the actual treatment received.

- *Safety Analysis Population*: Consists of all randomized subjects that received at least one dose of the assigned treatment according to the treatment received.

Per protocol population is based on the actual deviations, the criteria for exclusion of subjects from the different data sets will be specified and updated, if necessary, prior to database lock.

10.3 Planned Analyses

All efficacy and safety endpoint parameters will be summarized descriptively. Continuous efficacy and safety endpoints will be summarized using the mean, standard deviation, median, minimum and maximum, 25 and 75 percentiles). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints.

Once all patients complete the study evaluation (i.e., nominal study Week 24 or 26) or prematurely discontinued and the final database is locked, the study will be unblinded and final analyses will be performed. Analysis will be based on nominal study visits (i.e., study Weeks 0 to 26).

The primary efficacy hypothesis tests will be performed using a 2-sided 0.05 significance level. For secondary endpoints, adjustments for the overall type I error will be performed.

It is anticipated that statistical summaries will be performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC, USA) or higher. Additional software may be used to produce graphics and for statistical methodology not available in SAS.

10.3.1 Subject Disposition

An accounting of study subject disposition, including total number of subjects screened, enrolled, randomized, early discontinuation of study, and study completers, will be presented by treatment group. In addition, a flow diagram detailing the disposition of subjects will be created. Also, a listing with the reasons for screen failures and study discontinuation will be provided.

10.3.2 Enrollment Exceptions and Protocol Deviations

Major protocol deviations related to study inclusion or exclusion criteria, conduct of the trial, subject management or subject assessment will be listed by site. Major protocol deviations are deviations that may significantly affect the completeness, accuracy, and/or the reliability of the study data or that might significantly affect a subject's rights, safety and well-being. Examples of major protocol deviations are:

- Subject enrolled who does not meet eligibility criteria
- Subject who used non-permitted rescue medications
- Improper collection of or failure to collect the initial study informed consent
- Subject who received treatment that was contrary to their randomization assignment
- Subject who developed withdrawal criteria during the study but was not withdrawn.

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

10.3.3 Demographic and Baseline Characteristics

Baseline and demographic characteristics such as age, weight (kg), height (cm), body mass index (kg/m2), ethnicity, race, sex, disease type (i.e., primary or secondary), duration of AIHA, Baseline corticosteroid use (Yes/No), number of unique prior AIHA therapies, prior AIHA therapies, splenectomy (Yes/No), rituximab (Yes/No), hemoglobin (g/dL), LDH (U/L), reticulocyte (10^9/L), and haptoglobin (g/L) , at Baseline will be summarized by treatment group for the ITT population.

For continuous variables, number of observations, mean, median, standard deviation, minimum and maximum values, and 25th and 75th percentiles will be presented. For categorical variables, counts, and percentages will be tabulated for each category.

All randomly assigned subjects will be included in the analysis. Missing values will not be imputed.

10.3.4 Treatment Compliance

Subject compliance with the assigned treatment will not be collected in the EDC system. The assessment of compliance will be based on site monitoring and pharmacy drug dispensation logs. All pharmacy logs will be kept in the trial master file.

10.3.5 Concomitant Therapy

All medication used after the first protocol treatment to the end of study (Week 24/26) will be documented. Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary. Prior medications that are ongoing at the time of study enrollment will also be recorded. All concomitant medications will be listed and summarized by treatment group.

10.3.6 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is achievement of durable hemoglobin response (Yes/No) defined as achieving a hemoglobin level ≥ 10 g/dL with an increase from Baseline in hemoglobin level of ≥ 2 g/dL on 3 consecutive available visits during the 24-week treatment period, in which hemoglobin measurements eligible for this definition occurred outside a Rescue Treatment Visit Exclusion Period.

Available visits are defined as any scheduled visit where a plasma sample was collected, and hemoglobin level analyzed using either central or local laboratory.

For permitted rescue medications, a Rescue Treatment Visit Exclusion Period begins with the initiation of the rescue medication. The end of a Rescue Treatment Visit Exclusion Period is 4 weeks (28 days) following the return of steroid use to Baseline level or the last administration of rescue medication, whichever event occurs the latest. Any hemoglobin measurements made during this exclusion period are not eligible for any endpoint definition.

For non-permitted rescue medications, a Rescue Treatment Visit Exclusion Period begins with the initiation of the rescue medication and ends at Week 24/Week 26 or date of early termination from study.

If durable hemoglobin response cannot be determined because the subject discontinued from the study prior to attaining a durable response, then the subject will be assumed as not having achieved a durable response.

Analysis will be performed after all randomized subjects have completed the 24 weeks of treatment or discontinued from the study. All subjects randomized will be included in the analysis (ITT population). The following hypothesis will be evaluated:

H_o: $\Theta_{Fostamatnib,Placebo} = 1$

H_a: $\Theta_{Fostamatnib,Placebo} \neq 1$,

where $\Theta_{Fostamatnib,Placebo}$ is the odds ratio of durable hemoglobin response due to treatment.

Analysis will be performed using Cochran-Mantel-Haenszel (CMH) test stratified by concomitant steroid use at Baseline ($\geq$ 20 vs. < 20 mg daily), and screening hemoglobin level (< 9 vs. $\geq$ 9 g/dL). The odds ratio will be presented along with the 95% CI. The study will be considered to meet its primary efficacy objective if the lower bound of the 95% CI of the odds ratio of durable hemoglobin response between the Fostamatinib and Placebo-treated subjects is greater than 1.

In addition, the exact Clopper-Pearson 95% CI for the proportions and the Agresti-Min exact unconditional CI for the difference in proportions will be estimated.

The difference in proportion of durable hemoglobin response between the two treatment groups will be estimated and the 95% Miettinen-Nurminen score CIs[15)] will be computed taking into account the stratification factors.

A variety of sensitivity analyses of the primary analysis will be performed. These sensitivity analyses will consider:

- adjusting for prognostic variables for which an imbalance existed between the treatment groups at Baseline
- durable hemoglobin response derived using the hemoglobin values imputed
- changing the 4-week washout period in a Rescue Treatment Visit Exclusion Period to a 6-week washout period

Details will be provided in the SAP.

10.3.7 Analysis of Secondary Efficacy Endpoints

The secondary endpoints for this study are: hemoglobin response on at least one visit (Yes/No), achievement of change from Baseline in hemoglobin level ≥ 2 g/dL (Yes/No), change in hemoglobin values from Baseline to End of Treatment (Week 14 to Week 24), the use of permitted rescue medications after Week 4 (Yes/No), and change from Baseline to Week 24 in Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-F).

Adjustment for multiple testing using the hierarchical method as described in Section 10.4.

The proportion of subjects who achieve hemoglobin response on at least one visit, proportion of subjects who achieve a change from Baseline in hemoglobin level ≥ 2 g/dL, and proportion of subjects using permitted rescue medications after Week 4 will be summarized. All subjects randomized will be included in the analysis (ITT population). Subjects with no assessment for hemoglobin response will be treated as non-responders. Subjects with no assessment for change from Baseline in hemoglobin level will be treated as failure to achieve a change from Baseline in hemoglobin level ≥ 2 g/dL.

Analysis of hemoglobin response on at least one visit, change from baseline in hemoglobin level ≥ 2 g/dL, and use of rescue medications after Week 4 will be performed using the CMH test stratified by concomitant steroid use at Baseline (≥ 20 vs. < 20 mg daily), and Screening hemoglobin level < 9 vs. ≥ 9 g/dL). In addition, the exact Clopper-Pearson 95% CI for the overall proportions will be estimated by treatment group. In addition, the Agresti-Min exact unconditional 95% CI for the difference in proportions will be estimated as well as the 95% Miettinen-Nurminen score CIs [12] taking into account the stratification factors.

Change in hemoglobin value from Baseline to End of Treatment (Week 14 to Week 24) will be summarized using descriptive statistics, such as mean, standard deviation, and 95% CI. For each of the 200 imputed datasets in each imputation setting, change from Baseline to End of Treatment in hemoglobin levels will be analyzed using an analysis of variance (ANOVA) model with concomitant steroid use at Baseline (≥ 20 vs. < 20 mg daily), Screening hemoglobin level (< 9 vs. ≥ 9 g/dL) and treatment group as fixed effect in the model. Least squares mean with the 95% CI for the mean will be constructed for each treatment group and for the differences between the treatment groups. Rubin's rules[18] will be implemented to combine the results from all imputed datasets to provide the overall p-value, 95% CI, and difference between the treatment groups.

The overall FACIT-F score (defined in Section 4.3) prorated for missing items will be calculated, and the change from Baseline in overall score will be summarized for each treatment group at Baseline, Week 12, and Week 24. The number of observations, mean, median, standard deviation, and minimum and maximum values, 25th and 75th percentiles, and 95% CIs will be presented. In addition, box plots will be presented by treatment group for both raw values and for change from Baseline to Weeks 12 and 24. Change from Baseline to Week 12 and Week 24 in the FACIT-F will be analyzed using Mixed effect model for repeated measures implemented by SAS PROC MIXED. The model will use change from Baseline in FACIT-F as a response variable and include the fixed categorical effects of treatment group, weeks (12 and 24),

interaction between treatment and weeks, concomitant steroid use at Baseline (≥ 20 vs. < 20 mg daily), Screening hemoglobin level (< 9 vs. ≥ 9 g/dL), and Baseline FACIT-F as a covariate.

10.3.8 Additional Efficacy and Pharmacoeconomic Analysis

The additional efficacy and pharmacoeconomic endpoints of this study are defined in Section 4.5 and details of the analyses are provided in the SAP.

All additional efficacy and pharmacoeconomic analyses will be compared at the 0.05 significance level. These analyses will be used to support the primary and secondary efficacy analysis, therefore, no adjustment for multiplicity will be performed.

10.3.9 Safety Analysis

Safety will be assessed by examination of TEAEs, TEAE of interest, extent of exposure, and changes from Baseline in laboratory values (e.g., selected hematology, chemistry) over time. Furthermore, changes in vital signs of pulse, blood pressure, temperature, and body weight will be monitored.

10.3.9.1 Treatment-Emergent Adverse Events and TEAE of Interest

Treatment-emergent adverse events will be coded according to MedDRA. TEAEs are defined as events that first occurred or worsened following first dose of study treatment administration. All adverse events recorded as occurring before study treatment administration will be considered Baseline conditions. Related TEAEs are events considered related to study treatment by the investigator (i.e., possibly related, probably related, or related).

The number of events, the number of subjects, and the percentage of subjects who experienced at least one TEAE, incidence rate adjusting exposure will be presented. In addition, TEAEs that are considered by the Investigator to be related to a study drug; TEAEs that lead to early withdrawals; and serious TEAEs will be summarized in the same manner. Frequent TEAEs, including preferred terms with an incidence rate of ≥ 5% and TEAEs of interest will also be summarized. TEAEs of interest include hypertension, neutropenia, gastrointestinal complaints (nausea, vomiting, diarrhea, and abdominal pain, both overall and separately), infection, and liver function test elevation.

10.3.9.2 Extent of Exposure

The number of doses of study drug dispensed will be computed for each subject. Summaries will be computed by treatment group based on the Safety Population. Furthermore, the number and percent of subjects experiencing a dose reduction, interruption, or discontinuation of study drug will be presented by treatment group. In addition, a listing of all TEAEs that result in a reduction, interruption, or discontinuation of study drug will be presented. Finally, the reason for drug reduction, interruption, and discontinuation will be tabulated and presented by subject in data listings.

10.3.9.3 Change from Baseline in Laboratory Values

For selected hematology and chemistry laboratory tests performed, change from Baseline will be calculated for each subject and study visit. Box plots indicating mean and median as well as the 25th and 75th percentiles, and/or spaghetti plots will be presented by treatment group and study visit for both raw values and changes from Baseline.

Summary statistics (i.e., mean, median, standard deviation, maximum, and minimum, 25th and 75th percentiles) for the actual values, changes from Baseline, and maximum value observed post treatment will be tabulated by treatment group and study week. In addition, shifts based on lab values classified per CTCAE criteria V 5.0 at Baseline (i.e., Study Week 0), the maximum grade observed, and the grade observed for the last value post Baseline will be tabulated. New Grade 3 CTCAE on treatment in selected laboratory results will be listed.

10.3.9.4 Deaths

All deaths that occur during the study will be summarized and listed.

10.3.9.5 Absolute Neutrophil Count

Absolute neutrophil count is scheduled to be evaluated at Baseline (i.e., prior to administration of first dose of treatment), and every 2 weeks post randomization (Week 2 to Week 24). Change from Baseline in ANC will be calculated for each subject and study visit. Missing values will be treated as missing.

Summary statistics (i.e., mean, median, standard deviation, maximum, and minimum, 25th and 75th percentiles) for the actual values, changes from Baseline, and maximum value observed post treatment will be tabulated by treatment group and study week. In addition, shifts based on the CTC grades for ANC at Baseline (i.e., Study Week 0), the maximum value observed, and the last value for the post Baseline will be tabulated.

10.3.9.6 Blood Pressure Over Time

Blood pressure (i.e., systolic and diastolic blood pressure) is scheduled to be evaluated at Baseline (i.e., prior to administration of first dose of treatment), and every 2 weeks post randomization (Week 2 to Week 24). Change from Baseline in systolic and diastolic blood pressure will be calculated for each subject and study visit. For subjects with multiple blood pressure measurements for the same visit, the mean value for the visit will be used as the raw value to calculate the change from Baseline. Missing values will be treated as missing.

Summary statistics (i.e., mean, median, standard deviation, maximum, and minimum, 25th and 75th percentiles) for the actual values, changes from Baseline, and maximum value observed post treatment will be tabulated for both systolic and diastolic blood pressure by treatment group and study week. In addition, shifts based on the ACC/AHA guideline in blood pressure results from normal, elevated, Stage 1 and Stage 2 at Baseline (i.e., Study Week 0) to normal, elevated, Stage 1 and Stage 2 for the maximum observed value, and the last value post Baseline will be tabulated.

10.3.9.7 Liver Function Tests Over Time

Changes from Baseline in ALT and AST will be calculated for each subject and study visit. Missing values will be treated as missing.

Summary statistics (i.e., mean, median, standard deviation, maximum, and minimum, 25th and 75th percentiles) for the actual values, changes from Baseline, and maximum value observed post treatment will be tabulated for liver function tests by treatment group and study week. In addition, shifts based on the CTC grades in ALT, AST, and total bilirubin from the Baseline (i.e., Study Week 0) to the maximum observed value, and the last value post Baseline will be tabulated.

10.3.10 Pharmacokinetic Analysis

Plasma concentrations of the active component of fostamatinib (R406) will be measured at Weeks 2, 4, 12, and 18. The timing of the PK sampling as well as the date, time, and dosage of the last dose of study drug will be recorded. Data will be summarized by visit in accordance with the administered dose and regimen. Descriptive statistics (n, mean, standard deviation, median, minimum, IQR) will be tabulated.

10.4 Multiple Comparisons/Multiplicity

Analysis of secondary endpoints will be performed only if the primary efficacy analysis is significant at the 0.05 level using the gatekeeping procedure. Secondary efficacy analyses and secondary outcomes will be used to assess the consistency of the primary efficacy analysis.

Adjustment for multiple testing will be performed using the hierarchical approach to control the overall Type I error for the study. If the primary efficacy endpoint is statistically significant, 5 secondary endpoints will be tested sequentially in the order as listed in Section 4.3 with the corresponding p-values of p1, p2, p3, p4 and p5, respectively. Given α=0.05, at any time if $p_i > \alpha$, i=1,2,3,4,5, testing will be stopped with no statistically significant differences for the i^{th} and later secondary endpoints. If testing continues to $p5 < \alpha$, all 5 endpoints will be considered statistically significant.

10.5 Independent Data Monitoring Committee

An independent DMC will be formed and constituted according to appropriate regulatory agency guidelines. The independent DMC will review the safety data periodically and provide recommendations according to the charter. Detailed information regarding the composition of the committee and its procedures will be provided in the DMC charter.

10.6 Handling of Dropouts or Missing Data

Handling of dropouts and missing data is detailed extensively in the SAP.

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 the Clinical Trial Agreement, ICH Guidelines for Good Clinical Practice (E6, R2), Declaration of Helsinki (1996), and applicable laws and regulations.

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 11.4). 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 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.

11.1 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), or other national and international regulations.

Rigel will not approve or 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).

11.2 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 affected without the mutual agreement of the investigator and Rigel.

11.3 Protocol Deviations, and Waivers

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Important deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety and well-being.

If an Important deviation has occurred, it is to be discussed with the Medical Monitor. The Medical Monitor will determine if the subject may continue in the study. All deviations will be documented and discussed with the investigator and as applicable be reported to the IRB/IEC.

No waivers or exemptions from the protocol-specified inclusion or exclusion criteria will be allowed.

11.4 Informed Consent

The ICF and process for obtaining informed consent must comply with US regulations (§ 21 CFR Part 50), as well as other applicable national and international laws, rules, and regulations, including, with regard to European participants, the General Data Protection Regulation of the European Union. 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.

11.5 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 sub-investigator (as designated on the Form FDA 1572 or equivalent) 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

12.1.1 Source Documentation Requirements

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 associated EDC data, 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 and data collected for each visit (e.g. blood pressure), ICFs, screening and enrollment logs, subject questionnaires, laboratory requisitions and reports, checklists, pharmacy dispensing records, data recorded from automated instruments, ECGs, and treatments or procedures pertaining to SAEs. The investigator must assure that all original source documents are available to support monitoring, auditing and regulatory inspection activities.

The Sponsor shall maintain the records for a period of 25 years.

12.2 Electronic Case Report Forms

Electronic Case Report Forms (eCRFs) will be used to collect the clinical study data required per the protocol. 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 a validated 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. In case of a protocol amendment, the eCRFs will be updated, if required, to align with the amended protocol as part of maintenance during study conduct. 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 (e.g., 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 GCPs. 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, study plans and regulatory guidelines. Training will be provided for key investigative personnel in all aspects of study conduct.

In order to ensure that 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, EMA, and other Regulatory Agencies have access to all original electronic and paper source documents (as described in Sections 12.1 and 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.

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 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 (e.g., ICH and GCP) and either Rigel's or Rigel's authorized representative's SOPs and working instructions. Data management and control processes and quality assurance specific to this study, including applicable SOPs and regulations, will be described in a data management plan.

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 ICH-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 or as required by country regulations. All other essential documentation will be retained by the investigator for at least 5 years after the end of the trial. Should the investigator/ Institution be unable to continue maintenance of subject files for the full-time period, 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; 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 (e.g., 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 Agency 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;
- 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.

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Appendix 1: 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

Appendix 2: Recommended Dose Modifications and Management of Specific Adverse Reactions

Adverse Reaction	Recommended Action
Hypertension	
US Sites: Stage 1: systolic between 130-139 or diastolic between 80-89 mmHg	• Initiate or increase dosage of antihypertensive medication for subjects with increased cardiovascular risk and adjust as needed until BP is controlled. • If the BP target is not met after 8 weeks, reduce study drug to next lower daily dose (refer to Table 5).
Sites outside of the US: Stage 1: systolic between 130-139 or diastolic between 80-89 mmHg	• Monitor, or initiate or increase dosage of antihypertensive medication for subjects with increased cardiovascular risk and adjust as needed until BP is controlled, in accordance with local standards. • If the BP target is not met after 8 weeks, reduce study drug to next lower daily dose (refer to Table 5).
Stage 2: systolic at least 140 or diastolic at least 90 mmHg	• Initiate or increase dosage of antihypertensive medication and adjust as needed until BP is controlled. • If BP remains 140/90 mmHg or higher for more than 8 weeks, reduce study drug to next lower daily dose (refer to Table 5). • If BP remains 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive therapy, interrupt or discontinue study drug.
Hypertensive crisis: systolic over 180 and/or diastolic over 120 mmHg	• Interrupt or discontinue study drug. • Initiate or increase dosage of antihypertensive medication and adjust as needed until BP is controlled. If BP returns to less than the target BP, resume study drug at same daily dose. • If repeat BP is 160/100 mmHg or higher for more than 4 weeks despite aggressive antihypertensive treatment, discontinue study drug.
Hepatotoxicity	
AST/ALT is 5 x ULN or higher and total BL is less than 2 x ULN	• Interrupt study drug. • Recheck LFTs every 72 hours: • If AST and ALT decrease, recheck until ALT and AST are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN; resume study drug at next lower daily dose (refer to Table 5). • If AST/ALT persist at 5 x ULN or higher for 2 weeks or more, discontinue study drug.
AST/ALT is 3 x ULN or higher and less than 5 x ULN	If patient is symptomatic (e.g., nausea, vomiting, abdominal pain): • Interrupt study drug. • Recheck LFTs every 72 hours until ALT/AST values are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN. • Resume study drug at next lower daily dose (refer to Table 5).
	If patient is asymptomatic: • Recheck LFTs every 72 hours until ALT/AST are below 1.5 x ULN) and total BL remains less than 2 x ULN. • Consider interruption or dose reduction of study drug if ALT/AST and TBL remain in this category (AST/ALT is 3 to 5 x ULN; and total BL remains less than 2 x ULN).

Adverse Reaction	Recommended Action
	• If interrupted, resume study drug at next lower daily dose (refer to Table 5) when ALT/AST are no longer elevated (below 1.5 x ULN) and total BL remains less than 2 x ULN. • If AST/ALT persist at 5 x ULN or higher for 2 weeks or more, discontinue study drug.
AST/ALT is 3 x ULN or higher and total BL >2 x ULN	• Check direct and indirect BL levels. If direct BL is >2x ULN then discontinue study drug, if only indirect BL is >2x ULN then monitor as above.
Elevated unconjugated (indirect) BL in absence of other LFT abnormalities	• Continue study drug since isolated increases in unconjugated (indirect) BL may be due to UGT1A1 inhibition or the underlying wAIHA disease.
Diarrhea	
Diarrhea	• Manage diarrhea using supportive measures (e.g., dietary changes, hydration and/or antidiarrheal medication) early after the onset until symptom(s) have resolved. • If symptom(s) become severe (Grade 3 or above), temporarily interrupt study drug. • If diarrhea improves to mild (Grade 1), resume study drug at the next lower daily dose (refer to Table 5).
Neutropenia	
Neutropenia	• If absolute neutrophil count decreases (ANC less than 1.0×10^9/L) and remains low after 72 hours, temporarily interrupt study drug until resolved (ANC greater than 1.5×10^9/L). • Resume study drug at the next lower daily dose (refer to Table 5).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BP = blood pressure; BL = bilirubin; ULN = upper limit of normal; LFT = liver function tests (AST, ALT, total Bi with fractionation if elevated, alkaline phosphatase); AST/ALT = AST or ALT

Appendix 3: Corticosteroid Dose Equivalents

Corticosteroid Doses Equivalent to 10 mg of Prednisone	
Dose:	**Steroid:**
1.2 mg	Betamethasone (long-acting)
1.5 mg	Dexamethasone (long-acting)
8 mg	Methylprednisolone (intermediate-acting)
8 mg	Triamcinolone (intermediate-acting)
10 mg	Prednisolone (intermediate-acting)
40 mg	Hydrocortisone (short-acting)
50 mg	Cortisone (short-acting)

Appendix 4: Restricted Medications Unrelated to AIHA

The list below is not an exhaustive list (the Sponsor's Medical Monitor should be consulted in the event of questions). Additional detail is provided in the SmPC (Section 4.5 Interaction with other medicinal products and other forms of interaction).

A current list is available online at https://drug-interactions.medicine.iu.edu/Main-Table.aspx

Strong Inhibitors of CYP3A4

Clarithromycin	Telithromycin	Ketoconazole
Itraconazole	Suboxone	Nefazodone
Ritonavir	Indinavir	Nelfinavir
Saquinavir		

Moderate Inhibitors of CYP3A

Verapamil	Aprepitant	Erythromycin
	Fluconazole	Diltiazem

CYP3A Inducers

Barbiturates	Efavirenz	Nevirapine
Troglitazone	Rifampin	Rifabutin
Carbamazepine	Enzalutamide	Modafinil
Oxcarbazepine	Phenobarbital	Glucocorticoids
Phenytoin	St. John's Wort	

Appendix 5: FACIT-F

FACIT Fatigue Scale (Version 4)

	Not at all	A little bit	Some-what	Quite a bit	Very much
I feel fatigued	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I feel listless ("washed out")	0	1	2	3	4
I feel tired	0	1	2	3	4
I have trouble starting things because I am tired	0	1	2	3	4
I have trouble finishing things because I am tired	0	1	2	3	4
I have energy	0	1	2	3	4
I am able to do my usual activities	0	1	2	3	4
I need to sleep during the day	0	1	2	3	4
I am too tired to eat	0	1	2	3	4
I need help doing my usual activities	0	1	2	3	4
I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
I have to limit my social activity because I am tired	0	1	2	3	4

Appendix 6: EQ-5D-5L

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

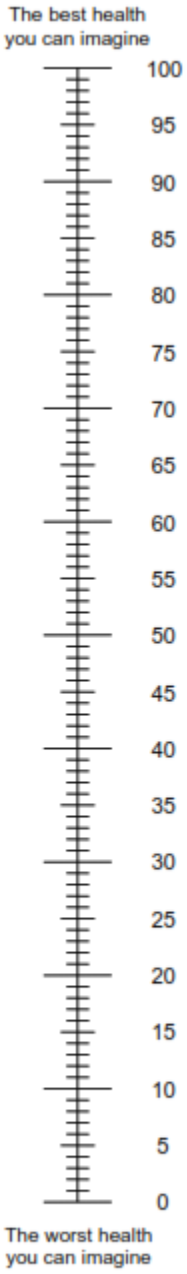
ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

2

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



3

Appendix 7: Management of Subject Visits During Pandemics

Screening:

Sites should not screen subjects if the subject is unlikely or unable to follow the protocol as written.

On Study Visits:

If possible, study patients should continue on study without interruption of the dosing and visit schedule.

If in-clinic visits are not possible, consideration can be given to continuing a subject on study drug without clinic visits as outlined below:

- Subjects should continue on study medication based on their safety and efficacy response to date (including an evaluation of all labs including ALT, AST, total and direct bilirubin (i.e., fractionated bilirubin), WBC, hemoglobin, hematocrit, and ANC; and any adverse events) up to 6-8 weeks without an in-person clinic visit. This is to be managed on a patient per patient basis at the discretion of the Investigator and in collaboration with the Medical Monitor.
- Subjects should have labs and blood pressure checked by their local physician/laboratory. Alternatives may include an at-home visit conducted by a study nurse. As a last resort, blood pressure may be checked with a home monitoring system and the site should contact subjects every 2 weeks to check for compliance and adverse events and any other information regarding their general status. Results should be shared with the Investigator for treatment decisions and documented in the medical record.
- If necessary, subjects may interrupt study drug and receive rescue treatment as needed for the underlying disease until restart of study drug, once in-clinic visits are resumed. Subjects are encouraged to stay on the study. The Investigator can consider this as a dose interruption. If an Investigator has concerns about a prolonged interruption, he/she should contact the Medical Monitor.
- Subjects reaching Week 24 visit who are unable to attend an in-clinic visit, should be discussed with the Medical Monitor.

Each patient has individualized needs and may miss an unknown number of visits, in the event of questions the Medical Monitor should be contacted.

Study Drug:

In accordance with regulations and institutional policies, study medication may be provided to subjects via courier. The medication should be dispensed per the RTSM system and sent to the subject via a traceable carrier with receipt confirmed by the subject.

Shipment or transport should take no longer than 72 hours. No temperature monitoring is needed during transit. Refer to the IB and pharmacy manual for full information on the stability of drug and dispensation instructions.

For sites sending medication per courier at regularly scheduled intervals or sending extra bottles: Subjects can be sent up to one extra bottle of drug.