CLINICAL PROTOCOL

A Phase 2, Multi-Center, Randomised, Double-Blind, Ascending-Dose, Placebo-Controlled Clinical Study to Assess the Safety and Efficacy of Fostamatinib in the Treatment of IgA Nephropathy

Protocol Number:	C-935788-050
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Sponsor Signature for Protocol C-935788-050

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

Daniel Magilavy, MD
Medical Monitor
Rigel Pharmaceuticals, Inc.

Mar 17, 2017
Date

Anne-Marie Duliege, MD
Chief Medical Officer
Rigel Pharmaceuticals, Inc.

MAR 17 2017
Date

Signature of Agreement for Clinical Protocol C-935788-050

I agree to the following:

- To conduct the study in strict accordance with this protocol and the contract with the Sponsor, Rigel Pharmaceuticals, Inc. (Rigel), and all applicable national and international laws, rules, and regulations, including the principles of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice and the Declaration of Helsinki.
- To maintain adequate and accurate records and make those records available for inspection by Rigel (or its authorized representative), 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 the requirements for obtaining informed consent and IRB/IEC review and approval are met.
- To comply with all other requirements regarding the obligations of Investigators as described in this protocol and in applicable laws.
- That this protocol and all data and information generated in connection with this study are the exclusive property of Rigel.

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

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

Investigator's Signature **Date**

Print Investigator's Name and Title

TABLE OF CONTENTS

1.0 PROTOCOL SYNOPSIS 8
2.0 ABBREVIATIONS AND TERMS 15
3.0 INTRODUCTION 17
3.1 Background 17
3.2 Rationale for Development of Fostamatinib for IgAN 18
3.3 Fostamatinib Safety and Pharmacokinetics 18
3.3.1 Single Ascending Dose Safety and Pharmacokinetics 18
3.3.2 Multiple-dose Pharmacokinetics 19
3.3.3 Metabolism 19
3.3.4 Renal Impairment Population 19
3.3.5 Drug-Drug Interactions 20
3.4 Efficacy 21
3.5 Safety 21
3.5.1 Blood Pressure Elevation 21
3.5.2 Liver Function Test Abnormalities 22
3.5.3 Neutropenia 22
3.5.4 Gastrointestinal (GI) Effects 22
3.5.5 Rare Adverse Events 23
3.5.6 Safety Summary 23
4.0 STUDY OBJECTIVES AND ENDPOINTS 24
4.1 Objectives 24
4.2 Primary Efficacy Endpoint 24
4.3 Secondary Efficacy Endpoints 24
4.4 Safety Endpoints 25
4.5 Pharmacokinetic Endpoints 25
4.6 Exploratory Histologic Endpoints 25
5.0 STUDY DESIGN 26
5.1 Summary of Study Description 26
5.2 Rationale for Proposed Dosing 27
5.3 Study Treatment 28
5.3.1 Randomisation 28

5.4 Safety Monitoring 28
5.5 Safety Review Committee 28
5.6 Administrative Structure 28
6.0 SUBJECT SELECTION 30
6.1 Inclusion Criteria 30
6.2 Exclusion Criteria 31
7.0 STUDY PROCEDURES 33
7.1 Screening (Visits 1a and 1b) 36
7.1.1 Screening Visit 1a 36
7.1.2 Screening Visit 1b 36
7.2 Treatment Period Visits 2-9 37
7.2.1 Baseline/First Dose (Visit 2) 37
7.2.2 Treatment Visits 3-9 37
7.3 Study Follow-Up (Visit 10) 38
7.4 Dose Adjustments Due to Adverse Events 38
7.4.1 Non-Diarrhoea Gastrointestinal Toxicity 39
7.5 Definition of Study Procedures 39
7.5.1 Medical History 39
7.5.2 Histologic Assessment of Renal Biopsies 39
7.5.3 Physical Exam 40
7.5.4 Vital Signs 41
7.5.5 Clinical Laboratories 41
7.5.6 Pregnancy Tests 41
7.6 Concomitant Therapies 42
7.6.1 Required Medications: Angiotensin Blockade 42
7.6.2 Restricted IgA Nephropathy Medications 42
7.6.3 Restricted Medications Unrelated to IgA Nephropathy 42
7.7 Pharmacokinetics Samples 42
7.8 Calculation of Blood Draws 42
7.9 Withdrawal from Study 43
7.10 Study Completion and Early Termination 44
7.11 Post-Trial Access to Fostamatinib 44
7.11.1 Dose Modification During Extended Treatment Period 45

8.0 STUDY DRUG 46
8.1 Study Drug Description 46
8.1.1 100 mg Tablets 46
8.1.2 150 mg Tablets 46
8.2 Storage 46
8.3 How Supplied/Study Drug Dispensation 46
8.4 Study Drug Administration 47
8.5 Unblinding 47
8.6 Study Drug Accountability/Drug Compliance 47
9.0 ADVERSE EVENTS 49
9.1 Definitions 49
9.2 Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators 52
9.2.1 Adverse Event Reporting Period 52
9.2.2 Assessment of Adverse Events 52
9.2.3 Expedited Reporting Requirements for Serious Adverse Events 53
9.2.4 Reporting of Serious Adverse Events by Sponsor 53
9.3 Pregnancy 53
10.0 STATISTICAL METHODS 55
10.1 General Considerations 55
10.2 Analysis Populations 55
10.3 Analysis of Efficacy Endpoints 55
10.3.1 Primary Efficacy Endpoint 56
10.3.2 Secondary Efficacy Endpoints 56
10.4 Analysis of Safety 57
10.5 Analysis of Pharmacokinetic Endpoints 58
10.6 Analysis of Exploratory Endpoints 58
10.7 Determination of Sample Size 58
10.8 Handling of Dropouts and Missing Data 58
10.9 Interim Analysis of Results from 100 mg bid Cohort 59
11.0 ETHICAL AND LEGAL ISSUES 60
11.1 Confidentiality of Subject Personal Information 60
11.2 Independent Ethics Committee/Institutional Review Board 60

11.3 Changes to the Study 61
11.4 Protocol Deviations, Violations, Waivers and Exemptions 61
11.5 Informed Consent 61
11.6 Liability, Insurance, and Financing 62
12.0 DATA COLLECTION, RETENTION, AND MONITORING 63
12.1 Source Data 63
12.1.1 Source Documentation Requirements 63
12.2 Electronic Case Report Forms 63
12.3 Monitoring 63
12.4 Data Quality Assurance 64
12.5 Data Collected by Contractors 64
12.6 Availability and Retention of Investigational Records 64
13.0 SUPERVISION OF THE STUDY 66
14.0 DISCLOSURE/PUBLICATION OF DATA 67
15.0 REFERENCES 68

LIST OF APPENDICES

Appendix 1: Guideline for Dose Modification for Possible Drug-Induced Liver Injury (DILI): AST or ALT 3x ULN or TBL > 2xULN 69
Appendix 2: Guideline for Management of Neutropenia 71
Appendix 3: Guideline for Management of Diarrhoea 72
Appendix 4: Guideline for Management of Hypertension 74
Appendix 5: Restricted Medications 76

LIST OF TABLES

Table 1: Double-Blind Treatment 28
Table 2: Schedule of Study Procedures—Main Study (Visits 1 through 10) 34
Table 3: Schedule of Study Procedures—Extended Treatment 35
Table 4: Dose Adjustment 39
Table 5: Oxford Classification of Renal Biopsy Scoring 40
Table 6: Number and Volume of Blood Samples and Total Blood Volume Collected per Subject (Screening through Follow-Up, and Extended Treatment Period) 43

LIST OF FIGURES

Figure 1: Study Design 27

1.0 PROTOCOL SYNOPSIS

Name of Finished Product(s):	Fostamatinib (R788)

Title of Study: A Phase 2, Multi-Center, Randomised, Double-Blind, Ascending-Dose, Placebo-Controlled Clinical Study to Assess the Safety and Efficacy of Fostamatinib in the Treatment of IgA Nephropathy

Objectives:

- To assess the efficacy of fostamatinib administered orally for 24 weeks to subjects with IgA nephropathy, as measured by change in renal function and histology.
- To investigate the safety and tolerability of fostamatinib administered orally for 24 weeks to subjects with IgA nephropathy.

Methodology: This is a Phase 2, multi-center, randomised, double-blind, ascending-dose placebo-controlled, proof-of-concept study to evaluate 2 dose regimens of fostamatinib in approximately 75 subjects. The study will consist of 11 visits over 28 to 43 weeks.

Subjects who meet all inclusion/exclusion criteria will be required to have completed at least 90 days of treatment with an angiotensin converting enzyme inhibitor (ACEi) and/or angiotensin II receptor blocker (ARB) at a maximum approved (or tolerated) dose and to have had a pre-study renal biopsy no more than 180 days prior to the initial study visit. The renal biopsy will be reviewed by a member of the central panel of renal pathologists to ensure subjects meet histological entry criteria.

The enrollment plan for this study has been to randomise patients in an ascending dose fashion, with review and approval of safety, tolerability and renal function findings by the Safety Review Committee prior to enrollment into Cohort 2. Once randomisation of the initial cohort of approximately 38 subjects (25 randomised to fostamatinib 100 mg *bid*, 13 to placebo) was complete, enrollment began for the second cohort of approximately 37 subjects (25 randomised to fostamatinib 150 mg *bid*, 12 to placebo). Subjects will be randomised 2:1 in each cohort so as to maintain 1:1:1 allocation for all 3 double-blind dosing groups (25 subjects per group; Table 1). Subjects will be stratified among the 3 treatment groups by presence or absence of endocapillary hypercellularity as determined by a member of the central panel of renal pathologists on the most recent renal biopsy obtained prior to randomisation.

Table 1: Double-Blind Treatment

Treatment Group	Number of Subjects	Dose
A	25	Fostamatinib 100 mg *bid*
B	25	Fostamatinib 150 mg *bid*
C	25	Placebo *bid*

During the 24-week double-blind treatment period, subjects should remain on the same dose of ACEi or ARB during the treatment period (Visits 2-9). Subjects will be monitored by

routine safety assessments (vital signs, haematology, serum chemistries, urinalyses, and adverse event [AE] assessments) and for renal function (spot urine protein/creatinine ratio [sPCR], urine dipstick test for haematuria and estimated glomerular filtration rate [eGFR] using the MDRD equation). At the end of the treatment period, subjects will be encouraged to have a renal biopsy.

Brief Summary of Visit Schedule

There will be 11 visits over the course of 28 to 43 weeks:

- Visit 1a = Up to 120 days prior to Baseline (Visit 2)
- Visit 1b = Up to 30 days prior to Baseline (Visit 2)
- Visit 2 = Day 1, Baseline
- Visit 3 = Week 1 ± 1 day, Treatment Week 1
- Visit 4 = Week 2 ± 3 days, Treatment Week 2
- Visit 5 = Week 4 ± 3 days, Treatment Week 4
- Visit 6 = Week 8 ± 4 days, Treatment Week 8
- Visit 7 = Week 12 ± 4 days, Treatment Week 12
- Visit 8 = Week 18 ± 7 days, Treatment Week 18
- Visit 9* = Week 24 ± 7 days, Treatment Week 24
- Visit 10 = Week 26 ± 3 days, Post-treatment

*Visit 9 procedures will be performed for subjects that withdraw early, with the exception that renal biopsy will not be required.

Prior to the completion of this study (ie, before the clinical database is locked and unblinded, and top line efficacy results are available), subjects who have had at least a 40% decrease from Baseline in proteinuria at Visit 9 (or, in the judgment of the Rigel Medical Monitor, a clinically significant improvement in post-treatment biopsy score) and have tolerated study drug may be permitted to continue to receive extended treatment with study drug (fostamatinib or placebo) on the same double-blind treatment regimen until the results of this study are known.

If the sPCR of a subject increases during the extended treatment period to more than 50% greater than the Week 24 value across 2 evaluations at least 2 weeks apart (whether analyzed at the local or central laboratory), the subject may be transitioned to 150 mg fostamatinib *bid* (whether previously receiving placebo, 100 mg fostamatinib *bid*, or 150 mg fostamatinib *bid*) if, in the Investigator's judgment, the subject has not experienced safety or tolerability issues related to study drug. The subject's original treatment during the 24-week main study and extended treatment period will remain double-blind until the end of the study.

Additional safety visits will occur at 2, 4, and 8 weeks from the treatment transition to 150 mg *bid* before the subject re-assumes the standard 12-week visit interval.

Number of Subjects: Approximately 75 subjects at 25 sites in 8 countries in Europe, Asia, and North America will be enrolled in the study.

Study Population: For the purpose of this study, the term 'subject' will refer to patients with IgA nephropathy (IgAN) participating in this study.

Inclusion Criteria:

1. Signed informed consent prior to any study specific screening procedures.
2. Male or female between 18 to 70 years of age (*Note: minimum age is 20 years in Taiwan and 21 years in Singapore)*.
3. Females must be either post-menopausal for at least 1 year, surgically sterile, or, if of childbearing potential, must not be pregnant or lactating. If sexually active, 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.
4. A pre-study renal biopsy obtained within 180 days prior to the initial study visit (Visit 1a) will be reviewed by a member of the central panel of renal pathologists to ensure subjects meet the following histologic entry criteria:
   - Consistent with IgAN
   - Mesangial hypercellularity score of > 0.5 (M1) and/or presence of endocapillary hypercellularity (E1) on renal biopsy (using the Oxford Classification). *Note: Subjects may be included with prior written permission from the Rigel Medical Monitor if the renal biopsy is graded M0 E0 but shows mesangial hypercellularity with a score of ≤ 0.5 or if there are less than 8 evaluable glomeruli on the submitted pre-study renal biopsy.*
   - ≤ 50% of cortical area involved by tubular atrophy or interstitial fibrosis (T0 or T1)
   - < 50% glomerular crescents

   Note: biopsies obtained greater than 180 days prior to Visit 1a may be permitted with prior written permission from the Rigel Medical Monitor if, according to the Investigator, there has been no clinically significant change in renal status.
5. Treatment with an ACEi and/or an ARB for at least 90 days at a maximum approved (or tolerated) dose prior to Screening (Visit 1b). *Subjects should remain on the same dose of ACEi or ARB during the treatment period (Visits 2-9).*
6. Proteinuria > 1 gm/day, sPCR > 100 mg/mmol (> 884 mg/g), or Spot Albumin/Creatinine Ratio > 70 mg/mmol at diagnosis of IgAN or any time prior to screening.
7 Proteinuria > 0.50 gm/day [sPCR > 50 mg/mmol (> 442 mg/g)] at Screening (Visit 1b). For USA only: proteinuria > 1 gm/day [sPCR > 100 mg/mmol (> 884 mg/g)] at Screening (Visit 1b) for Cohort 2 (150 mg *bid* or placebo).

8. Blood pressure controlled to ≤ 130/80 with angiotensin blockade with or without other anti-hypertensive agents. Subjects should be taking a maximum approved (or tolerated) dose of an ACEi or ARB before an additional anti-hypertensive agent is added. If additional anti-hypertensive therapy is required, other agents (beta-blockers, calcium channel blockers, or diuretics) may be added. Patients may be reassessed if BP < 140/90, but > 130/80.
9. Otherwise in stable health as determined by the Investigator based on medical history and laboratory tests during the screening period. See Exclusion Criteria for specific exclusions.
10. In the Investigator's opinion, 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. History of or active, clinically significant, respiratory, gastrointestinal (including pancreatitis), 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.
2. Have had any major cardiovascular event within the 180 days prior to randomisation, including but not limited to: myocardial infarction, unstable angina, cerebrovascular accident, pulmonary embolism, or New York Heart Association Class III or IV heart failure.
3. Diagnosis or history suggestive of Henoch-Schonlein purpura.
4. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (using the MDRD equation) at the time of Screening (Visit 1b).
   Note: Values as low 25 mL/min/1.73 m^2 may be permitted with prior written permission from the Rigel Medical Monitor if, according to the Investigator, there has been no clinically significant recent change in renal status.
5. A 50% decrease in eGFR from most recent pre-study clinic visit to Visit 1b.
6. An absolute neutrophil count of < 1,500/µL, Hgb < 9 g/dL, ALT or AST of > 1.5x ULN, total bilirubin > 2.0 mg/dL at Visit 1b. The Investigator may reassess these laboratory abnormalities within 30 days after Screening (Visit 1b).
7. Acute gastrointestinal symptoms (eg, nausea, vomiting, diarrhoea) at Baseline (Visit 2). The subject may be reassessed after full recovery from the acute gastrointestinal illness.
8. Active bacterial or parasitic infections, including tuberculosis.
9. Serologic results suggestive of active hepatitis B or hepatitis C (subjects may be included if confirmed hepatitis C recombinant immunoblot assay negative or hepatitis C virus RNA negative [qualitative]), or subjects with suspected human immunodeficiency virus (HIV).

10. Use within 6 months prior to pre-study renal biopsy of cyclophosphamide, mycophenolate mofetil, azathioprine, or Rituximab (or other anti-B cell therapies). Those subjects who had been treated with an anti- B cell therapy must have a normal CD19 count by Visit 1b.
11. Use of > 15 mg/day prednisone (or other corticosteroid equivalent). For those subjects taking corticosteroids for renal indication, the daily dose should not change from Baseline (Visit 2) to the end of the study drug treatment (Visit 9).
12. Prior or current use of cyclosporine or tacrolimus.
13. Have a clinically significant infection, or who are known to have an active inflammatory process (other than IgAN) at the time of Screening (Visit 1b) or Baseline (Visit 2). The subject may be reassessed after recovery from an acute infection.
14. Currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days or 5 half-lives (whichever is longer) of Screening (Visit 1a).
15. Are unable or unwilling to follow instructions, including participation in all study assessments and visits.
16. Have a history of alcohol or substance abuse that, in the judgment of the Investigator, may impair or risk the subject's full participation in the study.
17. Have a condition or be in a situation that the Investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study.
18. Have a known allergy and/or sensitivity to the study drug or its excipients.

Investigational Product: Fostamatinib (100 mg and 150 mg tablets) and matching placebo

Route of Administration: Oral

Dose: 1 tablet PO or matching placebo

Frequency of Dosing: *bid*

Duration of Treatment: 24 weeks (extended treatment available to eligible subjects)

Statistical Methods:

Analysis Populations:

- Intent-to-Treat Population

  The Intent-to-treat (ITT) population will include all randomised subjects. All efficacy endpoints will be analyzed based on the ITT population, and subjects will be analyzed according to their randomised treatment assignment. The efficacy analyses based on the ITT population will be considered the primary efficacy analyses.

- Per-Protocol Population

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

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

  Baseline measurements will be the last measurement for the corresponding variable prior to the first randomised dose at Visit 2. For analysis of the primary efficacy endpoint, the main analysis will be performed with baseline defined as the average between Visit 2 and the most recent screening value prior to Visit 2 (a secondary analysis, with the Visit 2 value alone as baseline, will be performed).

- Safety Population

  The safety population will include all randomised subjects who received at least 1 dose of the allocated study drug. The safety population will be used for analysis of all safety assessments. The subjects will be analyzed as treated.

Primary Efficacy Endpoint:

- Mean change from Baseline of proteinuria as measured by sPCR at 24 weeks (Visit 9)

Secondary Efficacy Endpoints:

- Mean change from pre-treatment to post-treatment in mesangial hypercellularity on renal biopsies.
- Percentage of subjects with ≥ 50% reduction in sPCR from Baseline (Visit 2) at Week 24 (Visit 9).
- Percentage of subjects with ≥ 30% reduction in proteinuria from Baseline (Visit 2) at 24 weeks (Visit 9)
- Mean change from pre-treatment to post-treatment in endocapillary hypercellularity on renal biopsies.
- Mean change from pre-treatment to post-treatment in segmental sclerosis/adhesion score on renal biopsies.
- Mean change from pre-treatment to post-treatment in global glomerulosclerosis score on renal biopsies.
- Mean change from pre-treatment to post-treatment in tubulointerstitial scarring on

renal biopsies.

- Mean change from pre-treatment to post-treatment in cellular/fibrocellular crescent score on renal biopsies.
- Mean change from Baseline (Visit 2) of eGFR at 12 weeks (Visit 7).
- Mean change from Baseline (Visit 2) of eGFR at 24 weeks (Visit 9).
- Mean change from Baseline (Visit 2) of proteinuria at 12 weeks (Visit 7).
- Percentage of subjects with sPCR < 50 mg/mmol at 12 weeks (Visit 7).
- Shift in haematuria (dipstick test) from Baseline (Visit 2) at 12 weeks (Visit 7).
- Shift in haematuria (dipstick test) from Baseline (Visit 2) at 24 weeks (Visit 9).

Sample Size Calculation:

A sample size of 25 evaluable subjects in each of the 3 treatment groups will have an 80% power to detect a 43% reduction in proteinuria from Baseline (Visit 2) to 24 weeks (Visit 9) between the pooled fostamatinib and placebo groups, using a 2-sided t- test with $\alpha = 0.05$ and log-transformed data. This calculation assumes that the 3 treatment groups have the same mean and standard deviations of urinary protein/creatinine ratio at baseline (130 mg/mmol ± 120 mg/mmol) and that the values for the placebo group remain constant over 24 weeks. Treatment allocation ratio will be 1:2 for the placebo: combined fostamatinib groups.

A detailed statistical analysis plan will be developed as a separate document and will be finalized prior to database lock

Interim Analysis of Results from 100 mg *bid* Cohort

An interim analysis of safety data was conducted for a portion of the subjects in the 100 mg *bid* cohort prior to proceeding with the 150 mg *bid* cohort.

An interim analysis of safety and efficacy data was conducted for all data collected through Week 26/Follow-Up from the 100 mg *bid* cohort. Statistical methods for the interim safety and efficacy analysis were specified in the Statistical Analysis Plan.

2.0 ABBREVIATIONS AND TERMS

ACEi	Angiotensin Converting Enzyme inhibitor
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute Neutrophil Counts
ARB	Angiotensin II Receptor Blocker
AST	Aspartate transaminase
AUC	Area under the curve
bid	*bis in die* (twice daily)
BP	Blood pressure
CBC	Complete blood counts
CFR	United States Code of Federal Regulations
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
CL_{CR}	Creatinine Clearance
CRO	Contract Research Organization
CYP	Cytochrome P450
DSUR	Development Safety Update Report
eCRF	Electronic case report form
EDC	Electronic data capture
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
FcR	Fc receptor
GCP	Good clinical practice
GI	Gastrointestinal
H	Hour
HEENT	Head, eye, ear, nose, and throat
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
IEC	Independent Ethics Committee
IgAN	Immunoglobulin A Nephropathy
IRB	Institutional Review Board
ITT	Intent-to-treat

IV	Intravenous
IVIg	Intravenous immunoglobulin
IWRS	Interactive web response system
kg	Kilogram
L	Liter
LFT	Liver function tests
LOCF	Last observation carried forward
µg	Microgram
µL	Microliter
µM	Micromolar
MDRD	Modification of Diet in Renal Disease
mg	Milligram
OATP	Organic anion transporting peptide
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
SAE	Serious adverse event
SOP	Standard operating procedure
sPCR	Spot urine protein/creatinine ratio
SRC	Safety Review Committee
Syk	Spleen tyrosine kinase
$T_{½}$	Half life
T_{max}	Time of maximum plasma concentration
V_{ss}	Volume of distribution at steady state
WBC	White blood cell
WHO	World Health Organization
X ULN	Multiple of upper limit of normal

3.0 INTRODUCTION

3.1 Background

Rigel Pharmaceuticals, Inc. (Rigel) is developing fostamatinib (R788) for the treatment of IgA nephropathy (IgAN). Fostamatinib is a prodrug that is rapidly converted *in vivo* to R940406 (R406), a potent, relatively selective Syk inhibitor. For the past 5 years, Rigel and AstraZeneca focused their clinical investigation efforts with fostamatinib on a large program in rheumatoid arthritis (RA), comprising over 3,000 patient-years of treatment. The results of those studies showed that fostamatinib was effective in reducing the signs and symptoms of RA, improving functional outcome in RA, but ineffective in slowing bone destruction and joint erosion. As a consequence of not demonstrating radiographic improvement, AstraZeneca decided to cease development in RA and return the drug to Rigel. Based upon the extensive clinical experience, the safety profile of R788 is very well understood in RA. The most common side effects are diarrhoea and related gastrointestinal (GI) disturbances, and elevated blood pressure, which usually responds to conventional anti-hypertensive therapies. Refer to the Investigator's Brochure for descriptions of the safety reports from these studies.

Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis in developed countries and a major cause of end-stage kidney disease. The natural course of IgAN is variable and ranges from asymptomatic microscopic haematuria to progressive kidney failure culminating in the need for dialysis and kidney transplantation. A higher risk of loss of kidney function is associated with persistent proteinuria (> 1 gram/day), sustained hypertension (> 140/90 mm Hg), impaired glomerular filtration rate (GFR), and histologic lesions based on glomerular, vascular, tubular and interstitial features as defined by the pathological classification.

The defining hallmark of IgAN is the deposition of IgA in the glomerular mesangium. The deposited IgA is exclusively of the IgA1 subclass and it is deficient in its galactose modification. In IgAN patients, excess amounts in the serum of this abnormal poorly-galactosylated IgA1 appear to be the trigger for the production of glycan-specific IgG and IgA autoantibodies. These autoantibodies lead to the formation of circulating immune complexes containing IgA1 that accumulate in the glomeruli and activate mesangial cells to produce and release a variety of mediators that include angiotensin II, aldosterone, proinflammatory and profibrotic cytokines and growth factors. Over a prolonged period of time, the unrelenting action of these mediators cause renal injury resulting in hypertension, proteinuria, haematuria and reduced renal function.

Currently, therapeutic options for IgAN are limited. The sole recommendation by the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines is for the use of renin-angiotensin blocking agents to control blood pressure and reduce proteinuria. For the significant fraction of patients that fail to lower the proteinuria target to < 0.5-1 g/day despite maximal amounts of ACEi or ARB, treatment modalities including glucocorticoids and immunosuppressive agents are limited by side effects or inconclusive efficacy.

FcγR receptor signaling in monocytes, macrophages, and dendritic cells plays an important role in the initiation and propagation of antibody-mediated inflammatory responses. The activating FcγR receptor complexes have a signaling subunit, referred to as the FcRγ chain, whose phosphorylation subsequent to receptor activation results in the recruitment and activation of the Syk kinase. Syk kinase is an important component of the signaling system of activating Fc receptors and the B-cell receptor, ultimately culminating in the production and release of mediators of the inflammatory response. Positive immunostaining for both "total" Syk and for "activated" phosphorylated-Syk in the glomeruli of kidney biopsies from IgAN patients suggest the involvement of Syk in the pathogenesis of IgAN. R406, the active ingredient of fostamatinib, is a potent inhibitor of Syk activity and therefore has the potential to ameliorate renal injury induced by autoantibody-containing immune complexes.

3.2 Rationale for Development of Fostamatinib for IgAN

In several rodent models of antibody-mediated glomerulonephritis, inhibition of Syk by treatment with fostamatinib or its active metabolite R406 can both prevent renal injury and reverse established renal pathology. These models include Wistar-Kyoto rats in which nephritis was induced either by the intravenous injection of nephrotoxic serum [(1)] or immunizing with the recombinant rat protein non-collagenous domain of the α3 chain of type IV collagen, a model of Goodpasture's [(2)]; and in 2 inbred mouse strains that spontaneously develop glomerulonephritis: NZB/NZW F1 [(3)] and MRL/lpr. [(4)] In both of the murine strains, fostamatinib treatment reduced proteinuria, azotemia, kidney pathology (including glomerular crescents, mesangial proliferation, and interstitial fibrosis), and prolonged survival.

Moreover, the effect of R406 on the activation by IgA1 of primary human mesangial cells (HMC) was investigated. [(5)] IgA1 purified from IgAN patients, but not IgA1 from healthy subjects, significantly stimulated HMC to produce the mRNA and protein of the mediator chemokine monocyte chemotactic protein-1 (MCP-1). This production was inhibited by R406 in a dose-dependent manner. R406 treatment also reduced the IgA1-induced production from primary HMC of other multiple cytokines and chemokines tested (IL-6, IL-8, IP-10, RANTES and PDGF-BB). Similarly, R406 inhibited the proliferation of HMC stimulated with heat-aggregated IgA1 purified from IgAN patients. Corresponding effects were obtained using Syk mRNA knockdown with small interfering RNA. Together, the results suggest that R406 blocks the action of pathogenic IgA1 on human mesangial cells by inhibiting the signaling controlled by Syk.

3.3 Fostamatinib Safety and Pharmacokinetics

3.3.1 Single Ascending Dose Safety and Pharmacokinetics

R406 appeared rapidly in the systemic circulation after fostamatinib dosing, with median T_{max} ranging between 1 and 3 hours. Negligible levels of R788 were found in plasma. The terminal half-life of R406 ranged from 12 to 19 hours. Increasing the doses of fostamatinib tablets from 100 to 300 mg resulted in approximately dose-proportional increases in R406 exposure.

The geometric mean absolute bioavailability of R406 was estimated to be 54.6% (90% CI 42.5 to 70.3%) in a bioavailability study in which 10 healthy volunteers were given a single oral dose of

150 mg fostamatinib and a 100 mcg IV dose of radiolabeled R406. Following the IV dose of R406 the volume of distribution at steady state (V_{ss}) was determined to be 256 L and total clearance (CL) of R406 was determined to be 15.7 L/h.

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

3.3.2 Multiple-dose Pharmacokinetics

A 2- to 2.5-fold increase in R406 exposure (AUC) was seen at 160 mg *bid*, when Day 7 exposure was compared with Day 1. At 250 mg *bid*, a 3.3-fold increase in R406 AUC was observed on Days 7 and 20 over Day 1. The higher than unity accumulation ratio is, to a large extent, due to *bid* dosing for a compound with a relatively long half-life. A 3-fold increase in dose (from 100 to 300 mg *bid*) resulted in approximately 4-fold increase in steady-state exposure. Platelet aggregation studies were performed in the single and multiple dose PK studies; no effect on collagen or ADP-induced platelet aggregation at the highest doses tested were observed.

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

3.3.3 Metabolism

R406 was found to undergo both oxidation and direct glucuronidation in humans. No unique metabolite was found in humans and there were no major circulating metabolites (> 10% of R406) in plasma. Renal elimination of parent drug was ~20%.

3.3.4 Renal Impairment Population

The conclusion from a 24 subject, single dose PK study with fostamatinib conducted in subjects with either moderate impairment in renal function ($CL_{CR} \geq 30$ to < 50 mL/min), end-stage renal disease (ESRD) requiring dialysis, or normal renal function ($CL_{CR} \geq 80$ mL/min), was that renal impairment did not affect the PK of R406 to an extent that would be considered clinically relevant. Compared to subjects with normal renal function, R406 AUC was lower for moderate renal impairment (RI) and ESRD groups, with geometric least squares mean (glsmean) ratios of 78.36% and 73.83%, respectively. However, unbound AUC was similar between groups. C_{max} was lower for the moderate RI and ESRD groups, with glsmean ratios of 57.74% and 61.94%, respectively. Geometric mean $t_{1/2}$ was similar across groups and ranged from 19.6-23.8 hours. There were no statistically significant relationships between R406 PK and CL_{CR}. Renal clearance of R406 was negligible for all groups, with < 0.1% of the administered dose recovered in urine as unchanged R406. The amount of R406 N-glucuronide recovered in urine decreased with decreasing renal function, at 14.7 mg, 7.56 mg, and 0.518 mg for normal, moderate, and ESRD groups, respectively. Exposure was lower when fostamatinib was administered after

completion of a dialysis session compared to administration 2 hours before the start of dialysis. The amount of R406 cleared by dialysis, 0.216 mg (< 1% of the dose) was negligible.

3.3.5 Drug-Drug Interactions

3.3.5.1 Effect of Other Drugs on R406 Exposure

- A strong CYP3A4 inhibitor, ketoconazole, produced ~2-fold increase in exposure to R406, while a moderate inhibitor, verapamil, caused ~1.4-fold increase in R406 exposure. The magnitude of these interactions suggests that fostamatinib is not a sensitive CYP3A4 substrate and that there are alternate *in vivo* pathways of R406 metabolism in humans.
- A strong inducer of multiple CYP enzymes, rifampicin, decreased exposure to R406 to about 25% of that observed when fostamatinib is administered alone.
- Ranitidine, which increases gastric pH, did not have a clinically relevant effect on the PK of R406.
- Single dose of rosuvastatin and simvastatin did not have a clinically relevant effect on the PK of R406.

3.3.5.2 Effect of Fostamatinib on Exposure of Other Drugs

- Co-administration of fostamatinib increased mean exposure to both rosuvastatin (by 2.0-fold for AUC and 1.9-fold for C_{max}) and simvastatin acid (by 1.7-fold for AUC and 1.8-fold for C_{max}). [preliminary data] R406 and R788 are substrates for and/or inhibitors of transporters (P-gp and BCRP), cytochrome P450 (CYP3A4) and other enzymes (UGT1A1). R406 is a weak inhibitor of OATP1B1 *in vitro*; however, it is predicted as unlikely to have relevant effects *in vivo*. Adverse findings in a mouse transgenic model suggested the possibility of an interaction between R406 and rosuvastatin resulting in increased plasma and liver rosuvastatin levels in an animal model sensitive to rosuvastatin. An analysis of serious adverse events in the clinical safety data base from the completed and ongoing fostamatinib Phase 2 - 3 clinical studies was conducted, focusing on patients concomitantly using a statin, including rosuvastatin. The analysis included data from 3,048 patients in the long-term extension studies in RA, as well as from the Phase 2 oncology program (studies in B- or T-cell lymphoma, diffuse large B-cell lymphoma, solid tumours and immune thrombocytopenia) up to 19 April 2012. In total, 389 patients were on a statin, (41 on rosuvastatin) while participating in a study. The analysis of SAEs did not reveal a new or emerging signal, nor did liver function differ from that observed in the general patient population. There is no evidence to date to suggest that there is a difference in the safety risk for patients on a statin.
- Digoxin geometric mean AUC_{ss} and $C_{max,ss}$ increased by 37% and 70%, respectively, when co-administered with fostamatinib. This increase in exposure is likely due to R788's inhibition of intestinal P-gp, resulting in an increase in the oral bioavailability of digoxin. Therefore, it is recommended that the subject's blood digoxin level be monitored throughout the treatment period.

- The effect of fostamatinib on midazolam, a selective CYP3A4 substrate sensitive to interaction with CYP3A4 inhibitors, suggests that fostamatinib is a weak CYP3A4 inhibitor and clinically important interactions between fostamatinib and CYP3A4 substrates are unlikely.
- There appears to be an interaction between fostamatinib and ethinyl estradiol resulting in a modest increase in ethinyl estradiol exposure. There does not appear to be an interaction between fostamatinib and levonorgestrel.
- Fostamatinib did not affect the PK or PD of warfarin to a clinically relevant degree.
- Fostamatinib did not have a clinically relevant effect on the primarily CYP2C8 mediated metabolism of pioglitazone and does not appear to induce CYP2C8 *in vivo*.

3.3.5.3 Food Effect

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

3.4 Efficacy

No efficacy trials have been conducted in patients with IgAN.

3.5 Safety

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

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

3.5.1 Blood Pressure Elevation

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

In RA clinical trials, increases in blood pressure (mean ~2-4 mmHg) generally occurred early and were responsive to anti-hypertensive treatment. Patients with a history of hypertension

appeared to be at greater risk of developing an increase in blood pressure and experienced higher mean increases (~5-9 mmHg). A few patients have experienced severe elevated blood pressure (≥ 180 systolic and ≥ 110 diastolic). In these studies the blood pressure effect has been reduced or eliminated over time by timely and effective anti-hypertensive treatment.

3.5.2 Liver Function Test Abnormalities

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

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

3.5.3 Neutropenia

Dose-dependent decreases in neutrophil counts have been observed in the majority of studies with fostamatinib. Transient neutropenia (typically resolving within 5 to 7 days of discontinuation of fostamatinib) has been observed in RA patients receiving fostamatinib at doses ranging from 50 to 150 mg *bid*. Neutropenia was not observed to any significant degree in the Phase 2 and 3 ITP trials. Dose reduction has generally resulted in resolution of the neutropenia and permitted patients to remain on study drug for prolonged periods. To date there is no clear association between neutropenia and an increased risk of infection, and no evidence that treatment with fostamatinib increases the risk of opportunistic infection.

3.5.4 Gastrointestinal (GI) Effects

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

There have been 12 SAE reports consistent with pancreatitis in the completed clinical trials. Factors confounding the ability to determine relationship to fostamatinib have included gall bladder disease, and other medications such as anti-hypertensives and NSAIDs. All but 1 episode resolved. The 1 unresolved episode involved a subject who had dyslipidemia and was using NSAIDs and had a fatal outcome. The relationship between fostamatinib and pancreatitis, if any, remains unclear.

3.5.5 Rare Adverse Events

As of the finalization date of this version of the protocol, 1 confirmed case of Posterior Reversible Encephalopathy Syndrome (PRES) and another case of a patient with malignant hypertension and seizures whose MRI showed subtle signs of PRES had been reported. In 1 patient, onset of the event was 5 days after stopping drug. In the other patient, it was less than 1 week after starting drug. Both patients recovered. In addition, a single SAE report for a suspected case of Toxic Epidermal Necrolysis (TEN) was received from the Phase 3 clinical trial program. Symptoms began 18 days after stopping the drug; the patient had a complicated course and did not survive. Concomitant medications prior to the start of the event included methotrexate, folic acid, diclofenac and deflazacort.

3.5.6 Safety Summary

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

4.0 STUDY OBJECTIVES AND ENDPOINTS

4.1 Objectives

- To assess the efficacy of fostamatinib administered orally for 24 weeks to subjects with IgA nephropathy, as measured by change in renal function and histology.
- To investigate the safety and tolerability of fostamatinib administered orally for 24 weeks to subjects with IgA nephropathy.

4.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from Baseline of proteinuria, as measured by sPCR at 24 weeks (Visit 9).

4.3 Secondary Efficacy Endpoints

- Mean change from pre-treatment to post-treatment in mesangial hypercellularity on renal biopsies.
- Percentage of subjects with ≥ 50% reduction in sPCR from Baseline (Visit 2) at Week 24 (Visit 9).
- Percentage of subjects with ≥ 30% reduction in proteinuria from Baseline (Visit 2) at 24 weeks (Visit 9).
- Mean change from pre-treatment to post-treatment in endocapillary hypercellularity on renal biopsies.
- Mean change from pre-treatment to post-treatment in segmental sclerosis/adhesion on renal biopsies.
- Mean change from pre-treatment to post-treatment in global glomerulosclerosis score on renal biopsies.
- Mean change from pre-treatment to post-treatment in tubulointerstitial scarring on renal biopsies.
- Mean change from pre-treatment to post-treatment in cellular/fibrocellular crescent score on renal biopsies.
- Mean change from Baseline (Visit 2) of eGFR at 12 weeks (Visit 7).
- Mean change from Baseline (Visit 2) of eGFR at 24 weeks (Visit 9).
- Mean change from Baseline (Visit 2) of proteinuria at 12 weeks (Visit 7).
- Percentage of subjects with sPCR < 50 mg/mmol at 12 weeks (Visit 7).
- Shift in haematuria (dipstick test) from Baseline (Visit 2) at 12 weeks (Visit 7).
- Shift in haematuria (dipstick test) from Baseline (Visit 2) at 24 weeks (Visit 9).

4.4 Safety Endpoints

The safety endpoints will assess the safety and tolerability of fostamatinib as assessed by the incidence of adverse events, clinical laboratory results (haematology, serum chemistry, and urinalysis), vital signs, and physical examinations. Safety parameters of particular interest will include increases in blood pressure, adverse effects on liver function tests including transaminase elevations, diarrhoea, other GI symptoms and neutropenia.

4.5 Pharmacokinetic Endpoints

The PK endpoint of this study will be a preliminary assessment of the kinetics of fostamatinib in subjects with IgAN. Plasma concentrations of R406 will be summarized by visit using descriptive statistics including the number of subjects, arithmetic mean, standard deviation, geometric mean, median, minimum, maximum, and coefficient of variation for each treatment group.

4.6 Exploratory Histologic Endpoints

Change from pre-treatment to post-treatment of macrophage subsets, Syk, Phospho-Syk, Smad 6, and Smad 7.

5.0 STUDY DESIGN

5.1 Summary of Study Description

This is a Phase 2, multi-center, randomised, double-blind, ascending-dose, placebo-controlled, proof-of-concept study to evaluate 2 dose regimens of fostamatinib in approximately 75 subjects. The study will consist of 11 visits over 28 to 43 weeks. Subjects may be eligible for extended treatment with study drug as described in Section 7.11.

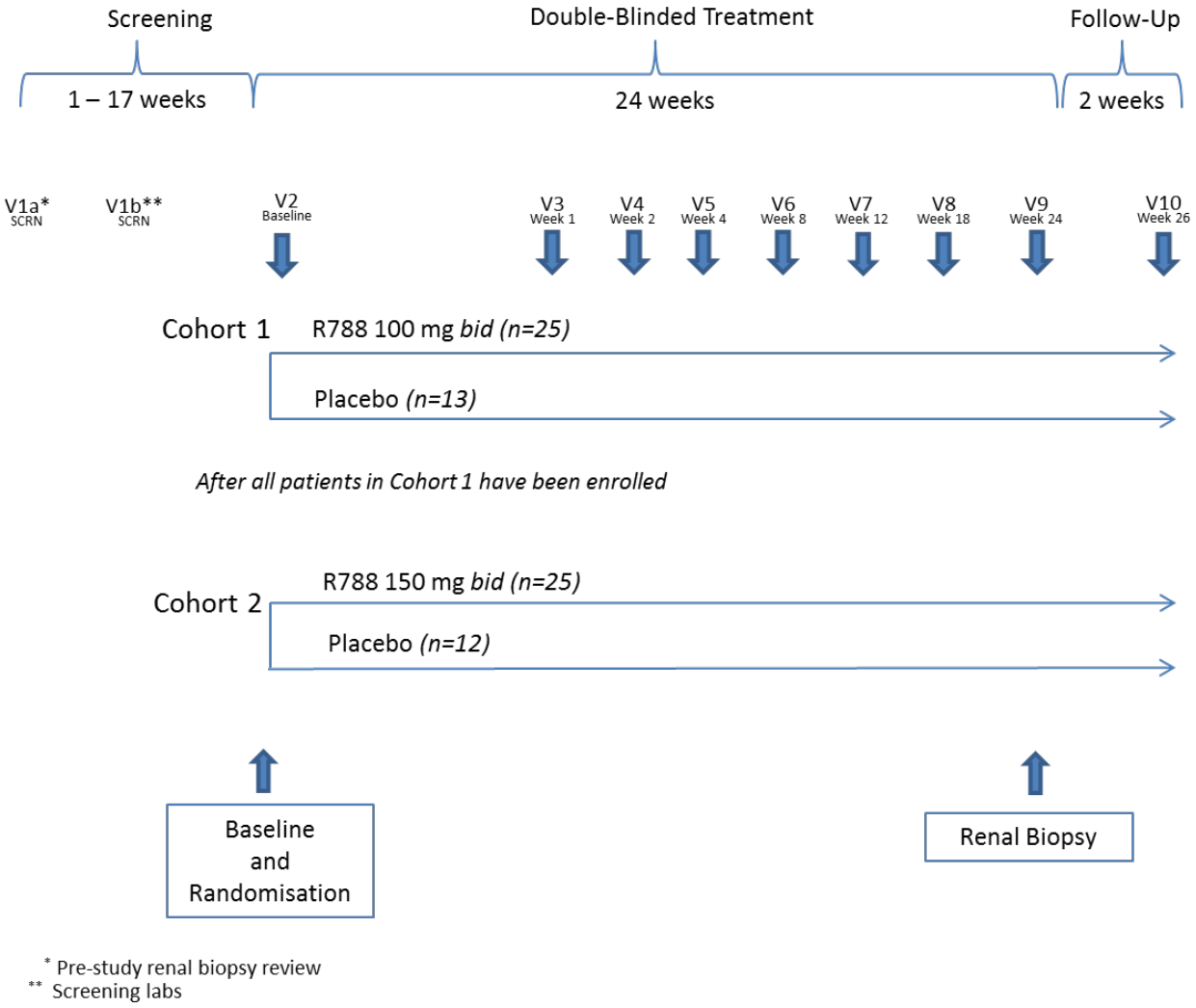
For the purpose of this study, the term 'subject' will refer to patients with IgAN participating in this study.

Subjects who meet all inclusion/exclusion criteria will be required to have completed at least 90 days of treatment with either an ACEi or ARB at a maximum approved (or tolerated) dose, and to have had a pre-study renal biopsy no more than 180 days prior to the initial study visit. The renal biopsy will be reviewed by a member of the central panel of renal pathologists to ensure subjects meet histological entry criteria (complete scoring by the full panel will occur following randomisation).

The enrollment plan for this study has been to randomise subjects in an ascending dose fashion with review and approval of safety, tolerability and renal function findings by the Safety Review Committee prior to enrollment into Cohort 2 (see Section 5.5). Once randomisation of the initial cohort of approximately 38 subjects (25 randomised to fostamatinib 100 mg *bid*, 13 to placebo) was complete, screening began for the second cohort of approximately 37 subjects (25 randomised to fostamatinib 150 mg *bid*, 12 to placebo). Subjects will be randomised 2:1 in each cohort so as to maintain 1:1:1 allocation for all 3 double-blind dosing groups (25 subjects per group: Table 1). Subjects will be stratified among the 3 treatment groups by presence or absence of endocapillary hypercellularity, as determined by a member of the central panel of renal pathologists on the most recent pre-study renal biopsy obtained prior to randomisation (see Figure 1).

During the 24-week double-blind treatment period, subjects should remain on the same dose of ACEi or ARB during the treatment period (Visits 2-9). Subjects will be monitored by routine safety assessments (vital signs, haematology, serum chemistries, urinalyses, and AE assessments) and for renal function (sPCR, urine dipstick test for haematuria and eGFR using the MDRD equation). At the end of the treatment period, subjects will be encouraged to have a renal biopsy.

Figure 1: Study Design



* Pre-study renal biopsy review
** Screening labs

After Visit 9 has been completed, subjects may be eligible for extended treatment with study drug (see Section 7.11).

5.2 Rationale for Proposed Dosing

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

In Phase 2 and 3 trials of fostamatinib in RA, multiple dose levels including 50 mg PO *bid*, 100 mg PO *bid* and 150 mg PO *qd* or *bid* were studied. 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. The average R406 exposure at 100 mg PO *bid* ranged from 4,400 to 7,020 ng•h/mL per dose interval, with daily exposures ranging from 8,800 to 14,000 ng•h/mL. These exposures are consistent with the levels needed to affect the Syk pathway, as defined in the biomarker assays described above, and support the 100 mg PO *bid* starting dose for this study.

5.3 Study Treatment

After qualifying during the screening period of the study, the initial cohort of subjects will be randomised in a 2:1 ratio to either fostamatinib 100 mg PO *bid* (see Table 1) or matching placebo. Screening may then begin at the next cohort in which subjects will be randomised in a 2:1 ratio to either fostamatinib 150 mg PO *bid* (see Table 1) or matching placebo.

Table 1: Double-Blind Treatment

Treatment Group	Number of Subjects	Dose
A	25	Fostamatinib 100 mg *bid*
B	25	Fostamatinib 150 mg *bid*
C	25	Placebo *bid*

5.3.1 Randomisation

An Interactive Web Response System (IWRS) will be used to randomise subjects to 1 of 2 groups in each cohort. The IWRS will assign a blister pack number of study drug to each subject who is eligible for the double-blind treatment period of the study. Subjects will be stratified at randomisation by the presence or absence of endocapillary hypercellularity on pre-study renal biopsy. An individual subject can only be randomised once for the entire study.

5.4 Safety Monitoring

The Rigel Medical Monitor and representatives will monitor the safety of study drug on an ongoing basis by assessing reported adverse events, vital signs, clinical laboratory values (haematology, serum chemistry, and urinalysis), and physical exams. In addition, subjects will be monitored for renal function (sPCR, and eGFR). Safety parameters of particular interest will include increases in blood pressure, adverse effects on liver function tests including transaminase elevations, diarrhoea, other GI symptoms and neutropenia.

5.5 Safety Review Committee

An independent Safety Review Committee (SRC) will monitor safety throughout the study.

In addition, the SRC, including one member who has IgAN expertise, evaluated the safety, tolerability and renal function findings prior to making a decision to proceed with dosing of Cohort 2 (150 mg *bid* or placebo).

5.6 Administrative Structure

This trial is sponsored by Rigel. Approximately 75 subjects will be randomised at 25 sites in 8 countries in Europe, Asia, and North America.

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

Data will be recorded in an electronic Case Report Form (eCRF) via an electronic data capture (EDC) system. An IWRS will be used for study drug inventory management and to randomise subjects to study drug. The central panel of renal pathologists will review renal biopsies to ensure subject eligibility, determine stratification (presence or absence of endocapillary hypercellularity) and evaluate endpoints with histologic criteria. A central laboratory will be used for testing haematology, serum chemistry, urinalysis, and serum pregnancy and will store PK samples. A bioanalytical laboratory will be used for testing pharmacokinetic (PK) samples.

6.0 SUBJECT SELECTION

6.1 Inclusion Criteria

1. Signed informed consent prior to any study specific screening procedures.

2. Male or female between 18 to 70 years of age (*Note: minimum age is 20 years in Taiwan and 21 years in Singapore)*.

3. Females must be either post-menopausal for at least 1 year, surgically sterile, or, if of childbearing potential, must not be pregnant or lactating. If sexually active, she 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.

4. A pre-study renal biopsy obtained within 180 days prior to the initial study visit (Visit 1a) will be reviewed by a member of the central panel of renal pathologists to ensure subjects meet the following histologic entry criteria:

    - Consistent with IgAN
    - Mesangial hypercellularity score of > 0.5 (M1) and/or presence of endocapillary hypercellularity (E1) on renal biopsy (using the Oxford Classification)
      Note: Subjects may be included with prior written permission from the Rigel Medical Monitor if the renal biopsy is graded M0 E0 but shows mesangial hypercellularity with a score of ≤ 0.5 or if there are less than 8 evaluable glomeruli on the submitted pre-study renal biopsy.
    - ≤ 50% of cortical area involved by tubular atrophy or interstitial fibrosis (T0 or T1)
    - < 50% glomerular crescents

    Note: biopsies obtained greater than 180 days prior to Visit 1a may be permitted with prior written permission from the Rigel Medical Monitor if, according to the Investigator, there has been no clinically significant change in renal status.

5. Treatment with an ACEi and/or an ARB for at least 90 days at a maximum approved (or tolerated) dose prior to Screening (Visit 1b). *Subjects should remain on the same dose of ACEi or ARB during the treatment period (Visits 2-9).*

6. Proteinuria > 1 gm/day, sPCR > 100 mg/mmol (> 884 mg/g), or Spot Albumin/Creatinine Ratio > 70 mg/mmol at diagnosis of IgAN or at any time prior to screening.

7. Proteinuria > 0.50 gm/day [(sPCR > 50 mg/mmol (> 442 mg/g)] at Screening (Visit 1b). For USA only: proteinuria > 1 gm/day [sPCR > 100 mg/mmol(> 884 mg/g)] at Screening (Visit 1b) for Cohort 2 (150 mg *bid* or placebo).

8. Blood pressure controlled to ≤ 130/80 with angiotensin blockade with or without other anti-hypertensive agents. Subjects should be taking a maximum approved (or tolerated) dose of an ACEi or ARB before an additional anti-hypertensive agent is added. If additional anti-hypertensive therapy is required, other agents (beta- blockers, calcium channel blockers, or diuretics) may be added. Patients may be reassessed if BP < 140/90, but > 130/80.

9. Otherwise in stable health as determined by the Investigator based on medical history and laboratory tests during the screening period. See Exclusion Criteria for specific exclusions.

10. In the Investigator's opinion, 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. History of or active, clinically significant, respiratory, gastrointestinal (including pancreatitis), 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.

2. Have had any major cardiovascular event within the 180 days prior to randomisation, including but not limited to: myocardial infarction, unstable angina, cerebrovascular accident, pulmonary embolism, or New York Heart Association Class III or IV heart failure.

3. Diagnosis or history suggestive of Henoch-Schonlein purpura.

4. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (using the MDRD equation) at the time of Screening (Visit 1b).
   Note: Values as low 25 mL/min/1.73 m^2 may be permitted with prior written permission from the Rigel Medical Monitor if, according to the Investigator, there has been no clinically significant recent change in renal status.

5. A 50% decrease in eGFR from most recent pre-study clinic visit to Visit 1b.

6. An absolute neutrophil count of < 1,500/µL, Hgb < 9 g/dL, ALT or AST of > 1.5x ULN, total bilirubin > 2.0 mg/dL at Visit 1b. The Investigator may reassess these laboratory abnormalities within 30 days after Screening (Visit 1b).

7. Acute gastrointestinal symptoms (eg, nausea, vomiting, diarrhoea) at Baseline (Visit 2). The subject may be reassessed after full recovery from the acute gastrointestinal illness.

8. Active bacterial or parasitic infections, including tuberculosis.

9. Serologic results suggestive of active hepatitis B or hepatitis C (subjects may be included if confirmed hepatitis C recombinant immunoblot assay negative or hepatitis C virus RNA negative [qualitative]), or subjects with suspected human immunodeficiency virus (HIV).

10. Use within 6 months prior to pre-study renal biopsy of cyclophosphamide, mycophenolate mofetil, azathioprine, or Rituximab (or other anti-B cell therapies). Those subjects who had been treated with an anti- B cell therapy must have a normal CD19 count by Visit 1b.

11. Use of > 15 mg/day prednisone (or other corticosteroid equivalent). For those subjects taking corticosteroids for renal indication, the daily dose should not change from Baseline (Visit 2) to the end of the study drug treatment (Visit 9).

12. Prior or current use of cyclosporine or tacrolimus.

13. Have a clinically significant infection, or who are known to have an active inflammatory process (other than IgAN) at the time of Screening (Visit 1b) or Baseline (Visit 2). The subject may be reassessed after recovery from an acute infection.

14. Currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days or 5 half-lives (whichever is longer) of Screening (Visit 1a).

15. Are unable or unwilling to follow instructions, including participation in all study assessments and visits.

16. Have a history of alcohol or substance abuse that, in the judgment of the Investigator, may impair or risk the subject's full participation in the study.

17. Have a condition or be in a situation that the Investigator feels may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject’s participation in the study.

18. Have a known allergy and/or sensitivity to the study drug or its excipients.

7.0 STUDY PROCEDURES

The study procedures to be performed at each visit are shown in Table 2 and Table 3.

Table 2: Schedule of Study Procedures—Main Study (Visits 1 through 10)

Study Procedure	Screening		Double-Blinded Treatment Period								Follow-Up
	Visit 1a	Visit 1b	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9/ Withdraw	Visit 10
	Up to 120 days prior to Baseline	Up to 30 days prior to Baseline	Day 1 (Baseline)	Week 1 (±3 days)	Week 2 (±3 days)	Week 4 (±3 days)	Week 8 (±4 days)	Week 12 (±4 days)	Week 18 (±7 days)	Week 24 (±7 days)	Week 26 (±3 days)
Informed Consent	X										
Demographic Information		X									
Medical History[1]		X	X								
Submit pre-study renal biopsy to central path for assessment[2]	X										
Physical Exam[3]		X	X	X		X	X	X	X	X	X
Inclusion/Exclusion		X	X								
Vital Signs[4]		X	X	X	X	X	X	X	X	X	X
Haematology[5]		X	X	X	X	X	X	X	X	X	X[10]
Serum Chemistry[6]		X	X	X	X	X	X	X	X	X	X[10]
Plasma Pharmacokinetics				X		X		X	X		
Serum Pregnancy[7]		X	X								
Urine for Pregnancy[7]			X		X	X	X	X	X	X	X
Urinalysis[8]		X	X	X	X	X	X	X	X	X	X[10]
Urine for sPCR		X	X	X	X	X	X	X	X	X	
Serum IgA			X					X		X	
Renal biopsy										X[11]	
Concomitant Medications		X	X	X	X	X	X	X	X	X	X
Adverse Event Evaluation[9]				X	X	X	X	X	X	X	X
Study Drug Accountability				X	X	X	X	X	X	X	
Dispense Study Drug			X	X	X	X	X	X	X		

[1] Medical History at Screening (Visit 1b) includes documentation of date of initial IgAN diagnosis, documentation of most recent renal biopsy, concomitant medications, documentation of angiotensin blockade treatment, prior medications for treatment of IgAN, and any other relevant medical condition.
[2] Histologic eligibility must be confirmed using the most recent biopsy obtained within 180 days prior to the initial study visit (Visit 1a) before performing any additional study specific screening procedures.
[3] Physical Examination includes HEENT, cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems. Baseline (Visit 2) will also include a measurement of height and weight.
[4] Vital Signs include blood pressure and heart rate measured as noted in Section 7.5.4.
[5] Haematology includes red blood cell count (RBC), white blood cell count (WBC), hemoglobin, hematocrit, WBC differential count (neutrophils, lymphocytes, eosinophils and basophils), MCHC, MCH, MCV, MPV, RDW, and platelet count.
[6] Serum Chemistry includes Na, K, Cl, CO_2, Ca, P, BUN, creatinine, globulin, glucose, ALT, AST, LDH, alkaline phosphatase, total bilirubin, direct bilirubin, indirect bilirubin, total protein and albumin.
[7] Females of childbearing potential only. Females who are either post-menopausal for at least 1 year or surgically sterile (documented by medical record) do not need to take pregnancy tests. In Austria only, at-home urine pregnancy testing will be completed at Week 15 and Week 21, as described in Section 7.5.6.
[8] Urinalysis includes appearance, glucose, ketones, blood, protein, nitrite, bilirubin, specific gravity, pH, urobilinogen, and leucocyte esterase. If positive for blood or protein trace, microscopy will be included.
[9] SAEs will be followed to resolution or stabilization unless the subject is lost to follow-up.
[10] Haematology, serum chemistry and urinalysis only performed at Week 26 (Visit 10) if there are clinically significant abnormalities identified at Week 24 (Visit 9).
[11] Visit 9 renal biopsy should be collected within 14 days of Visit 9, and is not required to be collected during this visit itself; Visit 9 biopsy will not be required for subjects that withdraw early.

Table 3: Schedule of Study Procedures—Extended Treatment

Study Procedure	Every 12 weeks (± 2 weeks) until study results available	Dose Modification Visits Following transition of subject to 150 mg fostamatinib *bid* [1]
		2, 4, and 8 weeks from dose modification
Informed Consent	X[2]	
Inclusion/Exclusion	X[2]	
Blood Pressure	X	X
Haematology[3]	X	X
Serum Chemistry[4, 5]	X	X
Urine for Pregnancy[6]	X	X
Urinalysis[5,7]	X	X
Urine for sPCR[5]	X	X
Concomitant Medications	X	X
Adverse Event Evaluation[8]	X	X
Study Drug Accountability	X	X
Dispense Study Drug[9]	X	

[1] If a subject transitions to 150 mg fostamatinib *bid* during the extended treatment period as defined in Section 7.11, visits will occur at 2, 4, and 8 weeks from the dose modification to confirm safety of the new treatment regimen. Starting 12 weeks after dose modification, the standard 12-week visit interval will resume.

[2] Prior to initiation of extended treatment, eligibility will be confirmed and eligible subjects will sign an informed consent addendum (see Section 7.11).

[3] Haematology includes red blood cell count (RBC), white blood cell count (WBC), hemoglobin, hematocrit, WBC differential count (neutrophils, lymphocytes, eosinophils and basophils), MCHC, MCH, MCV, MPV, RDW, and platelet count.

[4] Serum Chemistry includes Na, K, Cl, CO_2, Ca, P, BUN, creatinine, globulin, glucose, ALT, AST, LDH, alkaline phosphatase, total bilirubin, direct bilirubin, indirect bilirubin, total protein and albumin.

[5] Local (ie, standard care) proteinuria, serum creatinine, AST, ALT, bilirubin (total, direct, and indirect), alkaline phosphatase, and haematuria values may be collected in during the extended treatment period as defined in Section 7.11.

[6] Females of childbearing potential only. At-home urine pregnancy testing will be completed monthly, as described in Section 7.5.6. Females who are either post-menopausal for at least 1 year or surgically sterile (documented by medical record) do not need to take pregnancy tests.

[7] Urinalysis includes appearance, glucose, ketones, blood, protein, nitrite, bilirubin, specific gravity, pH, urobilinogen, and leucocyte esterase. If positive for blood or protein trace, microscopy will be included.

[8] SAEs will be followed to resolution or stabilization unless the subject is lost to follow-up.

[9] At dose modification visits, no new Study Drug will be dispensed; material from the prior 12-week interval visit will be re-dispensed following accountability.

7.1 Screening (Visits 1a and 1b)

Subjects must sign and date an Independent Ethics Committee/Institutional Review Board-(IEC/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 for study enrollment. Subjects who fail to meet eligibility criteria may be re-screened once if there is a reasonable expectation that the subject will be eligible after the repeat screen. Before a subject can be re-screened, approval must be obtained from the Medical Monitor. All screen and re-screen failures will be recorded in a Patient Screening Log. Any reasons for exclusion from the study will be documented.

7.1.1 Screening Visit 1a

After informed consent has been obtained (within 120 days prior to Baseline Visit 2), the most recent pre-study renal biopsy will be submitted to the central panel of renal pathologists to ensure subjects meet all histologic screening criteria and to determine stratification (presence or absence of endocapillary hypercellularity). The biopsy must be within 180 days prior to the initial study visit (Visit 1a). The site will be notified by the renal pathologists whether a subject meets histologic eligibility.

7.1.2 Screening Visit 1b

After histologic eligibility is confirmed and subject has received a minimum of 90 days of angiotensin blockade, the following will be obtained within 30 days prior to Baseline (Visit 2):

- Demographic information
- Medical history
- Concomitant medications
- Physical examination
- Vital signs
- Serum pregnancy test (for females of childbearing potential)
- Haematology
- Serum chemistry
- Urinalysis
- Urine for sPCR
- Evaluation of eligibility based on Inclusion/Exclusion criteria

7.2 Treatment Period Visits 2-9

7.2.1 Baseline/First Dose (Visit 2)

Baseline/First Dose (Visit 2) will occur within 30 days after Screening (Visit 1b).

To be eligible for randomisation into the study, subjects must continue to meet all inclusion/exclusion criteria. Females of childbearing potential must have a negative serum pregnancy test at Screening (Visit 1b) and Baseline (Visit 2). Administration of study drug need not await results of the Baseline (Visit 2) labs including the serum pregnancy test. A urine pregnancy will be obtained at Baseline (Visit 2) prior to randomisation to ensure female subjects of childbearing potential are not pregnant.

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

- Interim medical history
- Concomitant medications
- Physical examination including height and weight
- Vital signs
- Haematology
- Serum chemistry
- Serum IgA
- Urinalysis
- Urine for sPCR

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.

7.2.2 Treatment Visits 3-9

All visits subsequent to the baseline visit are determined by the date of the baseline visit and should occur within the visit windows specified in Table 2. Over the course of the 24 week treatment period, subjects will be expected to visit the clinic 8 times (including Baseline [Visit 2]). Safety assessments and renal function tests will be performed at each visit to evaluate the safety and efficacy of fostamatinib/placebo, and to determine if a dose adjustment is required. At Week 24 (Visit 9), a percutaneous renal biopsy will be performed and submitted to the central panel of renal pathologists for assessment. This end of treatment biopsy should be collected within 14 days of Visit 9, but is not required to be collected during the visit in which the rest of the Visit 9 procedures are performed. Subjects who withdraw from the study prior to Week 24 will, at discontinuation, have a withdrawal visit equivalent to the Week 24 (Visit 9) assessments (see Section 7.9), with the exception that the post-treatment biopsy will not be required.

In Austria only, at home urine pregnancy testing will be performed in Weeks 15 and 21 (see Section 7.5.6).

7.3 Study Follow-Up (Visit 10)

Subjects will be instructed to return to the clinic 2 weeks following the last dose of study drug for Follow-up Study assessments. Haematology, serum chemistry and/or urinalysis are to be performed only if there are clinically significant abnormalities identified in the corresponding panel at Week 24 (Visit 9). If an SAE is present at the last visit, follow-up should occur as indicated in Section 9.2.1.

7.4 Dose Adjustments Due to Adverse Events

Clinical testing to date has revealed 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:

- Increases in ALT, AST, or bilirubin (refer to Appendix 1 for guidance regarding LFT-related dose adjustments).
- ANC < 1000/mm^3 or 1.0 x 10^9/L (refer to Appendix 2 for guidance regarding management of neutropenia).
- Severe diarrhoea (refer to Appendix 3 for guidance regarding diarrhoea-related dose adjustments). [(6)]
- Hypertension uncontrolled by oral antihypertensive medications (refer to Appendix 4 for guidance regarding hypertension-related dose adjustments).
- Other severe or life-threatening adverse events considered related to study drug administration.

Subjects who have their dose reduced will not have their dose increased for the remainder of the study. When dose interruption or reduction is required, subjects and study staff will remain blinded to the original treatment allocation; however, subjects and study staff will be aware of the switch to a reduced dose level.

Subjects for whom dose reduction results in a once daily dose of fostamatinib or matching placebo will take the daily study drug dose in the morning. Table 4 details the strategy for dose adjustment in subjects who experience AEs requiring dose reduction.

Table 4: Dose Adjustment

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

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

7.4.1 Non-Diarrhoea Gastrointestinal Toxicity

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

7.5 Definition of Study Procedures

7.5.1 Medical History

Medical/surgical history will be taken at Screening and Baseline (Visits 1b and 2) and will include documentation of the date of initial IgAN diagnosis, documentation of most recent renal biopsy, concomitant medications, documentation of angiotensin blockade treatment, prior medications for treatment of IgAN and any other relevant medical condition. Any new relevant medical conditions between Screening and Baseline (Visits 1b and 2) will be documented as medical history.

7.5.2 Histologic Assessment of Renal Biopsies

Confirmation of the histologic eligibility from the most recent pre-study renal biopsy will be reviewed by a member of the panel of central nephropathologists using the Oxford classification of IgAN (and as defined in inclusion criterion 4). [(7)] In addition, the central nephropathologists will determine the degree of mesangial hypercellularity and absence or presence of endocapillary hypercellularity (the latter for stratification purposes). Biopsy slides will be prepared for shipment according to instruction in the Study Reference Manual and will be provided by sites to the central pathology panel with local pathology reports (with subject personal identifiers redacted). Biopsies will be analyzed as described below.

7.5.2.1 Assessment of Biopsies

The following data will be determined by the central pathology panel for each biopsy collected from a randomised subject:

- Total number of glomeruli (a minimum of 8)
- Number of glomeruli with global sclerosis

- Number of glomeruli with segmental sclerosis

For each glomerulus in the biopsy the following will be assessed (see Table 5):

- Mesangial hypercellularity
- Endocapillary hypercellularity (absent, segmental or global)
- Presence of crescents (cellular/fibrocellular or fibrous)

From the above assessments a MEST score will be calculated (see Table 5).

Slides will be stained immunohistochemically for CD68 and the number of positive cells in each glomerulus will be recorded, and from this the mean number of CD68 cells/glomerulus will be derived.

In addition, staining for Syk, Phospho-Syk, Smad 6, Smad 7 may be done.

Table 5: Oxford Classification of Renal Biopsy Scoring

Variable	Definition	Score
Mesangial hypercellularity	<4 Mesangial cells/mesangial area=0 ---------- 4–5 Mesangial cells/mesangial area=1 6–7 Mesangial cells/mesangial area=2 ≥ 8 Mesangial cells/mesangial area=3 ---------- *The mesangial hypercellularity score is the mean score for all glomeruli*	M0 ----- M1
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0-absent S1-present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0-absent E1-present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	T0-0-25% T1-26-50% T2->50%

7.5.3 Physical Exam

A physical exam should include evaluation of the head, eye, ear, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Physical examinations will include height and weight at Baseline (Visit 2) only. Physical examinations will be performed as per the study schedule in Table 2. Any new or worsened abnormalities should be recorded as medical history (prior to randomisation) or adverse events after randomisation (Baseline, Visit 2), if appropriate. No rectal or pelvic examination is required.

7.5.4 Vital Signs

Vital signs (including blood pressure and heart rate) will be assessed at study visits 1b through 10 and extended treatment period visits (blood pressure only). All blood pressure (BP) determinations should be made using an electronic sphygmomanometer with the subject seated. To minimize the 'white coat effect', the subject should rest in a quiet room for at approximately 10 minutes prior to taking the BP. The blood pressure should be taken at least 3 times at approximately 5-10 minutes apart, and the lowest of the 3 measurements will be recorded.

7.5.5 Clinical Laboratories

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

- Haematology: red blood cell count (RBC); white blood cell count (WBC), hemoglobin, hematocrit, WBC differential count, (neutrophils, lymphocytes, eosinophils and basophils), MCHC, MCH, MCV, MPV, RDW, and platelet count.
- Serum Chemistry: includes Na, K, Cl, bicarbonate (CO_2), Ca, P, BUN, creatinine, globulin, glucose, LDH, AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, indirect bilirubin, total protein, albumin.
- Serum IgA
- Urinalysis includes appearance, glucose, ketones, blood, protein, nitrite, bilirubin, specific gravity, pH, urobilinogen, and leucocyte esterase (leukocytes). If positive for blood or protein trace, then include microscopy.
- Spot urine for protein/creatinine ratio.

Clinically significant abnormal findings identified during the screening period should be recorded on the medical history eCRF as a diagnosis rather than recording actual laboratory values.

7.5.6 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 1b and 2). Subjects may be enrolled at Baseline (Visit 2) based on the urine pregnancy results. Urine pregnancy tests (performed at the site) will be obtained at Baseline and Weeks 4, 8, 12, 15 (Austria only), 18, 21 (Austria only), 24, and 26 (Visits 2, 5, 6, 7, 8, 9, and 10), and at each extended treatment period visit (see Section 7.11). During the extended treatment period (and, in Austria only, at Weeks 15 and 21 of the main study), female subjects of childbearing potential will also be provided with urine pregnancy test supplies to perform monthly self-testing between study visits, as permitted. Subjects who have a confirmed positive pregnancy test at any time during the study will be discontinued from the study and will be followed for safety (see Section 9.3).

7.6 Concomitant Therapies

Concomitant therapies will be recorded in the eCRF at Visits 1b through 10 and extended treatment period visits.

7.6.1 Required Medications: Angiotensin Blockade

Subjects should be taking a maximum tolerated approved dose of an ACEi or ARB before an additional anti-hypertensive agent is added. Subjects should remain on the same dose of ACEi or ARB during the dosing period (Visits 2-9). If additional anti-hypertensive therapy is required, other agents (beta-blockers, calcium channel blockers, or diuretics) should be added.

7.6.2 Restricted IgA Nephropathy Medications

Use of prednisone (or equivalent corticosteroids) is restricted to no more than 15 mg/day, and dosage should not change from Baseline (Visit 2) to the end of the study drug treatment (Visit 9). Mycophenylate mofetil, azathioprine, cyclophosphamide, cyclosporine, tacrolimus and Rituximab or other anti-B cell therapies are excluded during the course of this study.

7.6.3 Restricted Medications Unrelated to IgA Nephropathy

Due to the potential for drug-drug interactions with fostamatinib, specific treatments are either not allowed or are restricted during the course of this study (see Appendix 5).

7.7 Pharmacokinetics Samples

Blood samples for PK analysis will be drawn during the visits specified in Table 2. Date and time of last dose will be recorded. Samples will be shipped to and stored at the central laboratory during the course of the study. Samples will then be transferred to and analyzed at the corresponding bioanalytical laboratory.

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

7.8 Calculation of Blood Draws

The maximum amount of blood that will be collected during study Visits 1b through 10 for safety and PK assessments is shown in Table 6.

For subjects that qualify for the extended treatment period, approximately 7 mL of blood will be collected every 12 weeks (and at 2, 4, and 8 weeks after a one-time dose modification that may occur as defined in Section 7.11.1) for serum chemistry and haematology testing at the central laboratory.

Table 6: Number and Volume of Blood Samples and Total Blood Volume Collected per Subject (Screening through Follow-Up, and Extended Treatment Period)

Assessment	Maximum Number of Samples	Volume of Blood per Sample (mL)	Total Volume of Blood (mL)
Haematology	10 [a]	2	20
Serum chemistry	10 [a,b]	5	50
Serum pregnancy	2 [b]		
Serum IgA	3 [b]		
PK	4	4	16
Total volume of blood drawn from Screening through Follow-Up/ Week 26 (mL)			86
Extended treatment period visits (Haematology, Serum Chemistry)		7	7 mL per visit [c]

[a] Haematology or serum chemistry are to be performed at Week 26 (Visit 10) only if there are clinically significant abnormalities identified at Week 24 (Visit 9).

[b] Serum pregnancy (Visits 1b and 2) and serum IgA (Visits 1, 7, and 9) will be run from the serum chemistry sample.

[c] Extended treatment period visits occur every 12 weeks, with the exception of visits at 2, 4, and 8 weeks following a one-time dose modification for selected subjects as defined in Section 7.11.1. Blood collected for standard care assessments during the extended treatment period is not included in this calculation.

7.9 Withdrawal from Study

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

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

The reason for withdrawal must be noted on the eCRF.

Subjects who discontinue study drug will, at discontinuation, have a withdrawal visit equivalent to the Week 24 (Visit 9) assessments (post-treatment kidney biopsy will not be required). The reason for withdrawal must be noted on the eCRF. If an SAE is present at the withdrawal visit or at the subject's last participation in the study, the SAE should be followed as described in Section 9.2.1.

7.10 Study Completion and Early Termination

The study will end upon completion of all protocol procedures and achievement of study objectives. 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. If the Investigator becomes aware of any circumstances during the study that may reasonably indicate that the study should be terminated, the Investigator will immediately notify Rigel and will cooperate with Rigel in the investigation and evaluation of such circumstances and any decision of Rigel that may follow.

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

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

7.11 Post-Trial Access to Fostamatinib

Prior to the completion of this study (ie, before the clinical database is locked and unblinded, and top line efficacy results are available), subjects who have had at least a 40% decrease in proteinuria at Visit 9 from Baseline (or a significant improvement in post-treatment biopsy score, in the judgment of the Rigel Medical Monitor) and have tolerated study drug may be permitted to continue to receive study drug until the results of this study are known.

Following discussion of the extended treatment period activities, eligible subjects will sign an appendix to the informed consent. Treatment will continue for those subjects until this study is completed with the same double-blinded treatment administered during Visits 2 through 9 (including any dose reductions). Study drug will be dispensed every 12 weeks during the extended treatment period, provided subjects have no study drug-limiting toxicity and continue to receive clinical benefit in the opinion of the Investigator.

During the extended treatment period, haematology, serum chemistry, urinalysis, and sPCR will be analyzed at the central laboratory at every visit. For visits conducted prior to implementation of central laboratory testing in the extended treatment period, locally analyzed proteinuria, serum creatinine, AST, ALT, bilirubin (total, direct, and indirect) and alkaline phosphatase values collected closest to each extended treatment period visit will be recorded in the eCRF, if available (See Table 3 for Schedule of Procedures—Extended Treatment).

Females of childbearing potential will be provided with urine pregnancy test kits to self-administer monthly between visits as permitted, and will be tested at the site every 12 weeks

during extended treatment dispense visits, with results documented in the eCRF and monitored by the Sponsor.

Drug accountability (including any reasons for dose adjustment), concomitant medications, blood pressure, and information about any AE or pregnancy that occurs will be recorded in the eCRF. All other information regarding extended treatment with study drug will be recorded in each subject's chart according to local clinical practice.

If safety or tolerability issues are identified during the extended treatment period, the Investigator will follow the dose adjustment procedures as described in Section 7.4.

7.11.1 Dose Modification During Extended Treatment Period

If the sPCR of a subject increases during the extended treatment period to more than 50% greater than the Week 24 value across 2 evaluations at least 2 weeks apart (whether analyzed at the local or central laboratory), the subject may undergo a dose modification to 150 mg fostamatinib *bid* (whether previously receiving placebo, 100 mg fostamatinib *bid*, or 150 mg fostamatinib *bid*) if in the Investigator's judgment the subject has not experienced safety or tolerability issues related to study drug. The subject's original treatment during the 24-week main study and extended treatment period will remain double-blind until the end of the study.

Additional safety visits will occur at 2, 4, and 8 weeks from dose modification to 150 mg fostamatinib *bid* (procedures to be performed are identical to other extended treatment period visits before the subject resumes the standard 12-week visit interval at 12 weeks from the point of dose modification.

If a subject does not qualify for or is unwilling to undergo dose modification despite meeting the above criteria, the subject will be withdrawn from the study. In addition, if a subject undergoes dose modification and, after at least 8 weeks of treatment following dose modification, has 2 or more sPCR assessments that are more than 50% greater than the Week 24 value, the subject will be withdrawn. No withdrawal visit will be performed, but AE follow-up will occur as specified in Section 9.2.1.

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.

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

8.1.1 100 mg Tablets

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

Matching placebo tablets containing microcrystalline cellulose and sodium stearyl fumarate are supplied.

8.1.2 150 mg Tablets

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

Matching placebo tablets containing microcrystalline cellulose and sodium stearyl fumarate are supplied.

8.2 Storage

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

8.3 How Supplied/Study Drug Dispensation

Fostamatinib and matching placebo tablets are packaged into blister packs. Each blister pack will contain 34 tablets for 14 days of dosing (1 morning dose and 1 evening dose) plus 3 additional days. The appropriate number of blister packs will be assigned by the IWRS for a treatment period at each visit.

Drug will be dispensed as follows:

- At Baseline (Visit 2), 1 blister pack will be dispensed and subjects will be instructed to bring the blister pack containing unused study drug back to the clinic at Week 1 (Visit 3).

- At Week 1 (Visit 3), following accountability, the blister pack of study drug dispensed at Baseline (Visit 2) will be re-dispensed to cover dosing until Week 2 (Visit 4).
- At Week 2 (Visit 4), following accountability, 1 new blister pack will be dispensed to cover dosing until Week 4 (Visit 5).
- At Weeks 4 and 8 (Visits 5 and 6), following accountability, 2 blister packs will be dispensed.
- At Weeks 12 and 18 (Visits 7 and 8), following accountability, 3 blister packs will be dispensed.
- During the extended treatment period (for visits at 12 week intervals), following accountability, 6 packs will be dispensed. At Dose Modification Visits (see Section 7.11 and Table 3) blister packs will be re-dispensed following accountability.

Subjects will be instructed to return their blister pack(s) at each visit for drug accountability purposes.

8.4 Study Drug Administration

For *bid* dosing, subjects will self-administer 1 tablet twice daily by mouth: once in the morning and once in the evening. Morning and evening doses should be at least 8 hours apart and should be taken at approximately the same time each day.

For *qd* dosing, subjects will self-administer 1 tablet daily by mouth in the morning.

Tablets may be taken with or without food. Tablets should not be taken with grapefruit juice or other known CYP3A4 inhibitors (refer to Appendix 5). In the event of gastric upset, it may be useful to take tablets with food.

8.5 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 may be unblinded to disclose the identity of the study drug dispensed. Investigators seeking to unblind the subject's treatment assignment will contact the Rigel Medical Monitor, who will utilize the IWRS if unblinding is considered warranted by the Investigator. The IWRS 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. The Investigator must thoroughly document the circumstances surrounding the unblinding in the subject's medical record and in the eCRF.

Where direct Investigator-initiated unblinding access to the IWRS is required by the Competent Authority, the Rigel Medical Monitor must be notified of any unblinding, ideally prior to initiating the unblinding process but no later than 24 hours after the decision to unblind.

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

9.0 ADVERSE EVENTS

9.1 Definitions

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

For the purposes of this clinical study, AEs include only treatment emergent events which are either new or represent detectable exacerbations of pre-existing conditions. [8, 9]

AEs may include, but are not limited to:

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

The following are NOT considered an AE:

- **Pre-Existing Condition:** A pre-existing condition (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.
- **Pre-Planned Hospitalization:** A hospitalization planned prior to signing the ICF is not considered an SAE but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration but not performed prior to enrollment in the study will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Hospitalizations for social reasons or due to long travel distances are also not considered SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.

Serious Adverse Event (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 (eg, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.

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

Suspected Adverse Reaction:

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

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

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

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

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

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

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

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

Assessment of Severity

The following grading system should be used to assess severity:

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

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

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

The Investigator is responsible for ensuring that all AEs (including SAEs) that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported on the SAE Report Form (see Section 9.2.3 for further information).

9.2.1 Adverse Event Reporting Period

The AE reporting period begins with the first dose of study drug and ends with the final study (follow-up) visit. AEs that occur between the time of consent and first dose of study drug will be reported as Medical History.

If an SAE is present at the follow-up visit (Week 26, Visit 10) or final visit for subjects receiving extended treatment as described in Section 7.11.1, it should be followed to resolution or stabilization unless the subject is lost to follow-up. Resolution means the subject has returned to baseline state of health or the Investigator does not expect any further improvement or worsening of the event.

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

9.2.2 Assessment of Adverse Events

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

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

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

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

9.2.3 Expedited Reporting Requirements for Serious Adverse Events

An Investigator should report a SAE within 1 day (ie, immediately but no later than the end of the next business day) of his/her awareness of the event by completing and sending the provided SAE form to Rigel's authorized safety representative. [NOTE: In UK, SAEs must be reported within 24 hours.]

Additionally, all fatal or life-threatening SAEs should be telephoned to Rigel as soon as the Investigator learns of the event.

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

Email: clinsafety@rigel.com

Fax: see Study Reference Manual

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

Daniel Magilavy, MD
Medical Monitor
Rigel Pharmaceuticals, Inc.
Tel.: +1.650.624.1372
Mobile: +1.603.770.7216
Fax: +1.650.624.1282
E-Mail: dmagilavy@rigel.com

9.2.4 Reporting of Serious Adverse Events by Sponsor

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

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

9.3 Pregnancy

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

Prior to study enrollment, females of childbearing potential must agree in the ICF to take appropriate measures to avoid pregnancy at all times during the study, commencing from the

time of consent to 30 days after the last dose of study drug, and, if pregnancy occurs, they must agree to report the pregnancy and cooperate with the Investigator as set forth below.

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

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

10.0 STATISTICAL METHODS

10.1 General Considerations

The statistical analysis of the data obtained from this study will be performed using SAS® version 9.2 or higher. All inferential tests will be 2-sided and will be performed using a type I error rate of 5%, unless otherwise indicated.

A detailed statistical analysis plan will be developed as a separate document and will be finalized prior to database lock.

10.2 Analysis Populations

The Intent-to-Treat (ITT) population will include all randomised subjects. All efficacy endpoints will be analyzed based on the ITT population, and subjects will be analyzed according to their randomised treatment assignment. The efficacy analyses based on the ITT population will be considered the primary efficacy analyses.

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

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

For analysis of the primary efficacy endpoint, the main analysis will be performed with baseline defined as the average between Visit 2 and the most recent screening value prior to Visit 2 (a secondary analysis, with the Visit 2 value alone as baseline, will be performed). For all other analyses, baseline measurements will be the last measurement for the corresponding variable prior to the first randomised dose at Visit 2.

Safety and efficacy data from the extended treatment period will not be subjected to statistical analysis.

10.3 Analysis of Efficacy Endpoints

The number of subjects who were screened, enrolled into the study and completed the study through Visit 9 will be summarized by treatment group using all enrolled subjects. The reasons that treated subjects withdrew from the study will also be summarized. Efficacy data from the extended treatment period will not be included in the statistical analysis.

Subject demographic data (age, gender, race, ethnicity) will be summarized by treatment group using the Safety population, as will baseline characteristics of height and weight.

10.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from Baseline (Visit 2) of proteinuria as measured by sPCR at 24 weeks (Visit 9). This will be analyzed using an ANCOVA model in the ITT population. The ANCOVA model will include both the treatment group and the presence/absence of endothelial hypercellularity at baseline as factors and will adjust for the proteinuria at baseline (as a covariate). The urine protein-creatinine ratio will be log-transformed prior to analysis. Missing Week 24 (Visit 9) data will be imputed using a multiple imputation procedure to be described in the SAP.

10.3.2 Secondary Efficacy Endpoints

The safety population will include all randomised subjects who received at least 1 dose of the allocated study drug. The safety population will be analyzed for all safety assessments. The subjects will be analyzed as treated.

Secondary efficacy endpoints related to proteinuria will measured by sPCR (as is the case for the primary efficacy endpoint).

All secondary efficacy endpoints will be analyzed using both the ITT and PP populations. Additionally, the primary efficacy endpoint will be analyzed using the PP population as a sensitivity analysis. No adjustments will be made for multiplicity.

The following secondary endpoints will be analyzed using an ANCOVA model which includes the treatment group and presence/absence of endothelial hypercellularity at baseline as factors, with mean estimates of the variable adjusted for the baseline value:

- Mean change from pre-treatment to post-treatment in mesangial hypercellularity on renal biopsies.
- Mean change from pre-treatment to post-treatment in endocapillary hypercellularity on renal biopsies.
- Mean change from pre-treatment to post-treatment in segmental sclerosis/adhesion on renal biopsies.
- Mean change from pre-treatment to post-treatment in global glomerulosclerosis score on renal biopsies
- Mean change from pre-treatment to post-treatment in tubulointerstitial scarring on renal biopsies.
- Mean change from Baseline (Visit 2) of eGFR at 12 weeks (Visit 7).
- Mean change from Baseline (Visit 2) of eGFR at 24 weeks (Visit 9).
- Mean change from Baseline (Visit 2) of proteinuria at 12 weeks (Visit 7).
- Shift in haematuria (dipstick test) from Baseline (Visit 2) at 12 weeks (Visit 7).

- Shift in haematuria (dipstick test) from Baseline (Visit 2) at 24 weeks (Visit 9).

Estimates will be provided for the following contrasts: 1) combined fostamatinib group vs. placebo; 2); 150 mg fostamatinib group vs. placebo; and 3) 100 mg fostamatinib group vs. placebo.

Fisher's exact test will be used to assess whether the percentage of subjects who meet the following criteria differ between the pooled fostamatinib and placebo groups:

- Have a ≥ 30% reduction in sPCR from Baseline (Visit 2) to Week 24 (Visit 9)
- Have sPCR < 50mg/mmoL at Week 12

The 95% CIs for the percentages will also be provided.

Shift tables will display the change in category from Baseline (Visit 2) to Week 24 (Visit 9) for the following categorical parameters:

- Presence/absence of segmental sclerosis/adhesion
- Presence/absence of global glomerulosclerosis
- Presence/absence of tubulointerstitial scarring

Fisher's exact test will assess whether there is an association between the change in these categories from Baseline (Visit 2) to Week 24 (Visit 9) and treatment group (ie, combined fostamatinib group vs. placebo).

10.4 Analysis of Safety

All safety variables will be analyzed using the Safety population. The safety population will include all randomised subjects who received at least 1 dose of the allocated study drug. The safety population will be used for analysis of all safety assessments through Visit 10. Safety data from the extended treatment period will not be included in the statistical analysis.

The safety endpoints will assess the safety and tolerability of fostamatinib as assessed by the incidence of adverse events, clinical laboratory results (haematology, serum chemistry, and urinalysis), vital signs, and physical examinations. Safety parameters of particular interest will include increases in blood pressure, adverse effects on liver function tests including transaminase elevations, diarrhoea, other GI symptoms and neutropenia.

The safety outcomes of this study include the change from baseline in blood pressure, liver function, and absolute neutrophil count (ANC) and the incidence of GI complaints and infections, as well as the incidence of any adverse events.

For each treatment group, descriptive statistics will be presented by visit for the actual values and the changes from baseline for systolic and diastolic blood pressure, each liver function test (ALT, AST, alkaline phosphatase, and bilirubin [total, direct, and indirect]), and ANC.

The difference between fostamatinib and placebo in the mean change from baseline will also be presented for each endpoint. The numbers and percentages of subjects with GI complaints and infections at any time during the double-blind treatment period will be presented by treatment group for the Safety Population. Fisher's Exact Test will be used to test for a difference between fostamatinib and placebo in the proportions of subjects experiencing GI complaints and infections.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with at least 1 adverse event, at least 1 serious adverse event (SAE), and at least 1 treatment related adverse event will be presented by treatment group. AEs that are possibly or probably related to study treatment, or for which the relationship to study treatment is missing, will be considered treatment related. AEs will be summarized at the subject level by MedDRA system organ class (SOC) and preferred term using frequencies and percentages. AEs will also be tabulated at the event level by severity and by relationship to study treatment for each treatment group.

10.5 Analysis of Pharmacokinetic Endpoints

Plasma concentrations of R406 will be summarized by visit using descriptive statistics including the number of subjects, arithmetic mean, standard deviation, geometric mean, median, minimum, maximum, and coefficient of variation for each treatment group.

10.6 Analysis of Exploratory Endpoints

No inferential statistical analysis will be performed on the exploratory endpoints regarding change in histologic staining from pre-treatment to post-treatment renal biopsies (macrophage subsets, Syk, Phospho-Syk, Smad 6, Smad 7). Only descriptive statistics will be used.

10.7 Determination of Sample Size

A sample size of 25 evaluable subjects in each of the 3 treatment groups will have an 80% power to detect a 43% reduction in proteinuria from Baseline (Visit 2) to 24 weeks (Visit 9) between the pooled fostamatinib and placebo groups, using a 2-sided t-test with $\alpha = 0.05$ and log-transformed data. This calculation assumes that the 3 treatment groups have the same mean and standard deviations of urinary protein/ creatinine ratio (130 mg/mmol ± 120 mg/mmol) at Baseline (Visit 2) and that the values for the placebo group remain constant over 24 weeks. Treatment allocation ratio will be 1:2 for the placebo: combined fostamatinib groups.

10.8 Handling of Dropouts and Missing Data

For the primary endpoint analysis, missing Week 24 (Visit 9) values of sPCR will be imputed using a multiple imputation method to be specified in the SAP.

Missing data for the secondary endpoints will not be imputed.

10.9 Interim Analysis of Results from 100 mg bid Cohort

An interim analysis of safety data was conducted for a portion of the subjects in the 100 mg *bid* cohort prior to proceeding to the 150 mg *bid* cohort.

An interim analysis of safety and efficacy data was conducted for all data collected through Week 26/Follow-Up from the 100 mg *bid* cohort. Statistical methods for the interim safety and efficacy analysis were specified in the Statistical Analysis Plan.

11.0 ETHICAL AND LEGAL ISSUES

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

11.1 Confidentiality of Subject Personal Information

Information on the confidential treatment of subject personal information collected in the study must be provided to each subject in the Informed Consent (see Section 11.5). In addition, an authorisation for the collection, use, disclosure, and transfer of subject personal information (an "Authorisation"), 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.

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

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

11.2 Independent Ethics Committee/Institutional Review Board

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

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

The IEC/IRB must comply with national and international regulations.

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

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

2. A copy of the IEC/IRB-approved ICF (and Regulatory Authority-approved ICF, where applicable).

11.3 Changes to the Study

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

11.4 Protocol Deviations, Violations, Waivers and Exemptions

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

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

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

A protocol exemption is defined as:

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

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

11.5 Informed Consent

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

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

11.6 Liability, Insurance, and Financing

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

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

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

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

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

For all Rigel clinical studies, each Investigator and Subinvestigator will provide a signed Financial Disclosure Form. 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 paper and/or electronic source documentation to enable the subsequent verification of study data. Source documentation for this study may include, but not be limited to, original documents such as ICFs, subject questionnaires, laboratory reports, hospital and/or clinic or office records documenting subject visits, and treatments or procedures pertaining to SAEs. Entry of data into the eCRFs will comply with all applicable regulatory requirements to ensure the reliability, quality, integrity, and traceability of the electronic source data.

12.2 Electronic Case Report Forms

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

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

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

12.3 Monitoring

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

In order to ensure 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 Rigel or its authorized representative, and other regulatory authorities, have access to all original electronic and paper source documents (as described in Section 12.1 and Section 12.2) at reasonable times and upon reasonable notice. During the review of source documents, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations (refer to Section 11.1).

Monitoring visits will occur as required during the conduct of the study. The study monitor will physically visit the study site(s) at least 2 times during the study duration (interim and close out visits) or more, if deemed necessary, and will be allowed, on request, to inspect the various records of the study. The study monitor will contact the study site via telephone and written communication regularly throughout the conduct of the study to maintain current and personal knowledge of the study. It will be the study monitor's responsibility to remotely inspect the eCRFs at regular intervals throughout the study to verify 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 IEC/IRB with a final report and provide Rigel or its authorized representatives with a copy of the final report.

12.4 Data Quality Assurance

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

12.5 Data Collected by Contractors

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

12.6 Availability and Retention of Investigational Records

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

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

Essential documentation includes, but is not limited to: the Investigator's Brochure; signed protocol and amendments; signed Informed Consent; 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 IEC/IRB approval; normal laboratory values; decoding procedures for blinded studies; curricula vitae for study staff; and pertinent study-related correspondence. No study document or image (eg, scan, radiograph) 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 applicable national Regulatory Agencies may choose to inspect a study site at any time prior to, during, or after completion of the clinical study. In the event of such an inspection, Rigel will be available to assist in the preparation. All pertinent study data should be made available, as requested, to the Regulatory Authority for verification, audit, or inspection purposes.

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

13.0 SUPERVISION OF THE STUDY

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

14.0 DISCLOSURE/PUBLICATION OF DATA

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

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

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

The Investigator will submit to Rigel any proposed publication or presentation along with the name of the respective scientific journal or presentation forum at least 30 days prior to submission of the publication or presentation. The Investigator will comply with Rigel's request to delete references to its confidential information in any paper or presentation and agrees to withhold publication or presentation for an additional 60 days in order to obtain patent protection on the contents of any publication if deemed necessary by Rigel. This requirement should not be construed as a means of restricting publication but is intended solely to assure consonance 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: Guideline for Dose Modification for Possible Drug-Induced Liver Injury (DILI): AST or ALT 3x ULN or TBL > 2xULN

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

- **Note**: Fostamatinib is an inhibitor of UGT1A1, the enzyme responsible for the glucuronidation of bilirubin; occasionally an isolated increase in total and unconjugated (indirect) bilirubin may be observed. Study drug should not be held for an isolated increase in total and unconjugated (indirect) bilirubin.
- The study Medical Monitor should be notified immediately of any potential case meeting Hy's law criteria.

Table 1: Dose Adjustment

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

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

Identification

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

- Stop study drug treatment immediately and withdraw the subject from the study for possible drug-induced liver injury.
- Complete the appropriate LFT module of the case report form (CRF) with the original laboratory test results.
- Follow the subject until liver biochemistry parameters and any clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Sponsor's Medical Monitor.

If AST or ALT ≥ 3x ULN or total (and/or conjugated**)** bilirubin > 2x ULN, and the subjects are exhibiting the following symptoms: nausea, vomiting, abdominal pain:

- Withhold/ interrupt dosing with study drug immediately.
- Repeat LFTs, including bilirubin and alkaline phosphatase every 3 days/72 hours until ALT/AST or total (and/or conjugated) bilirubin returns to < 1.5x ULN.

- Complete the appropriate LFT module of the CRF with the original laboratory test result.
- When the ALT/AST or total (and/or conjugated) bilirubin returns to < 1.5x ULN, study drug may be restarted at dose level -1.

If AST or ALT ≥ 3x ULN or total (and/or conjugated) bilirubin > 2x ULN and subject is asymptomatic:

- Complete the appropriate LFT module of the CRF with the original laboratory test result.
- Repeat LFTs, including bilirubin and ALP, within 72 hours.
- If repeat testing shows an increase in ALT/AST or total (and/or conjugated) bilirubin and the ALT/AST value exceeds 5x ULN, hold dosing with the study drug.
- Repeat LFTs, including bilirubin and alkaline phosphatase every 3 days/72 hours until ALT/AST is decreasing, and should be followed until transaminase returns to < 1.5x ULN.
- In subjects for whom study drug is interrupted, upon return of ALT/AST or total (and/or conjugated) bilirubin to < 1.5x ULN, study drug may be restarted at dose level -1.

REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm006499.htm

Appendix 2: Guideline for Management of Neutropenia

Based on data from previous clinical studies, treatment with fostamatinib may be associated with lowering of absolute neutrophil count (ANC).

A decrease in ANC may require adjustment of the dose of study drug. Follow the dose adjustment guidelines in Table 1 and outlined below when adjusting the dose of study medication.

Table 1: Dose Adjustment

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

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

Decrease in absolute neutrophil count (ANC) to < 1,000/µL:

- Repeat ANC within 72 hours in the local laboratory.
- If repeat testing confirms that ANC is < 1,000/µL, hold study drug dosing.
    - Repeat ANC at 72 hour intervals.
- When ANC recovers to > 1,500/µL, restart study drug at dose level -1.

Second event of ANC < 1,000/µL:

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

Appendix 3: Guideline for Management of Diarrhoea

Diarrhoea

- Based on data from previous clinical studies, treatment with fostamatinib may be associated with diarrhoea.
- Subjects should be made aware that they may experience diarrhoea and instructed to contact the clinical site if they experience diarrhoea.
- In some circumstances it may be necessary to adjust the dose of study drug. Follow the dose adjustment guidelines in Table 1 and outlined below when adjusting the dose of study medication.

Table 1: Dose Adjustment

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

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

Grading of Severity of Diarrhoea: The US National Cancer Institute has introduced the following criteria for the grading of severity of diarrhoea: [(10)]

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

Grade 1 or 2 Diarrhoea

- Study drug may be continued.
- Discontinue all laxatives.
- Subjects should be instructed to drink 8-10 glasses of water or clear fluids per day.
- Subjects should be encouraged to make dietary changes including elimination of dairy products and eating smaller but more frequent meals.
- Consider stool sample for microbiologic evaluation and antibiotics if subject is neutropenic.

- Grade 1, consider initiating treatment with loperamide according to the regimen below (not to exceed a maximum of 20mg in 24 hours). Grade 2, initiate treatment with loperamide according to the regimen below:
    - 4 mg loperamide initial dose.
    - 2 mg loperamide after each subsequent loose stool.
- Subjects with persistent diarrhoea (> 48 hours) should be monitored carefully for dehydration and electrolyte imbalance.

Grade 3 or 4 Diarrhoea

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

Management of Second Event of Grade 3 and 4 Diarrhoea

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

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Appendix 4: Guideline for Management of Hypertension

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

Blood pressure for all subjects should be kept below 140/90 mmHg; for subjects with increased cardiovascular risk or renal insufficiency, consideration should be given to maintaining the blood pressure below 130/80 mmHg. Subjects should remain on the same dose of ACEi or ARB during the dosing period (Visits 2-9). If additional anti-hypertensive therapy is required, other agents (beta-blockers, calcium channel blockers, or diuretics) should be added. In previous clinical studies evaluating fostamatinib, the following anti-hypertensive agents (alone or in combination) have proven effective in managing BP:

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

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

Management Algorithm for Elevated Blood Pressure

Follow the dose adjustment guidelines in Table 1 when adjusting the dose of study medication.

Table 1: Dose Adjustment

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

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

The following should result in prompt discontinuation of study medication:

- The blood pressure cannot be brought under control despite best efforts at blood pressure management.

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

- Temporarily withhold dosing with study drug.
- Adjust anti-hypertensive medications.
- Reassess BP twice weekly.
- If a repeat BP ≥ 180/110 mmHg despite adjusted anti-hypertensive treatment, permanently discontinue study drug.
- Increase anti-hypertensive medications until control is established.
- Restart study drug (at a reduced dose, see Table 1) when blood pressure < 140/90 mm Hg.

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

- Continue study drug at assigned dose level.
- Adjust anti-hypertensive therapy.
- Reassess BP twice weekly.
- If, after 1 week, the BP remains ≥ 160-179 systolic or ≥ 100-109 diastolic despite aggressive antihypertensive therapy, interrupt study drug administration.
- Increase anti-hypertensive medications until control is established.
- Restart study drug (at a reduced dose, see Table 1) when blood pressure < 140/90 mm Hg.

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

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

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Appendix 5: Restricted Medications

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

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

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

Fostamatinib is known to increase the plasma concentration of the HMG-CoA reductase inhibitors simvastatin and rosuvastatin by 50-100%. If a subject develops muscle pain or weakness, the dose of HMG-CoA reductase may need to be lowered and the subject monitored closely for any adverse effects associated with myositis.

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

List of Inhibitors and Inducers of CYP3A4

The list below is not an exhaustive list (the Sponsor's Medical Monitor should be consulted in the event of questions).

Strong Inhibitors of CYP3A4

Clarithromycin	Telithromycin	Ketoconazole
Itraconazole	Fluvoxamine	Nefazodone
Ritonavir	Indinavir	Nelfinavir
Sequinavir	Atazanavir	

Moderate Inhibitors of CYP3A

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

CYP3A Inducers

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