STATISTICAL ANALYSIS PLAN

Protocol Number	C-935788-050
Protocol Title:	A Phase 2, Multi-Center, Randomized, Double-Blind, Ascending-Dose, Placebo-Controlled Clinical Study to Assess the Safety and Efficacy of Fostamatinib in the Treatment of IgA Nephropathy
Product:	Fostamatinib
Indication:	IgA Nephropathy
Development Phase:	2
SAP Version:	Version 3
Date:	22 March 2018

SIGNATURE PAGE FOR

A PHASE 2, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, ASCENDING-DOSE, PLACEBO-CONTROLLED CLINICAL STUDY TO ASSESS THE SAFETY AND EFFICACY OF FOSTAMATINIB IN THE TREATMENT OF IGA NEPHROPATHY

Sponsor:	Rigel Pharmaceuticals, Inc.
Study Numbers:	C935788-050
Version:	Version 3.0
Date:	22 March 2018

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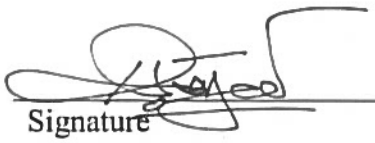

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1. Introduction

The purpose of this Statistical Analysis Plan is to outline the planned statistical analyses and presentation of the clinical data from Rigel Pharmaceuticals, Inc. Protocol C-935088-050: version 5.0 dated on 31 March 2017. Analysis covered in this document will cover the main study only. A separate plan will be provided for the extension study.

2. Study Objectives

The primary objectives of this study are:

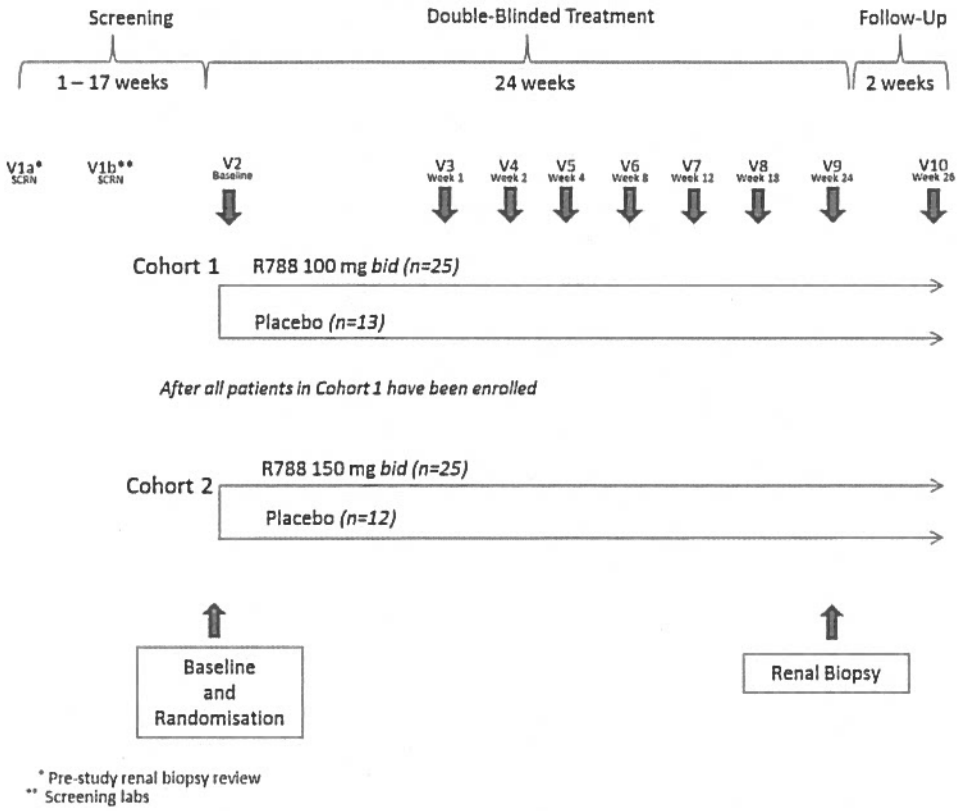
- To assess the efficacy of fostamatinib administered orally for 24 weeks to subjects with IgA nephropathy, as measured by change in renal function and histology.
- To investigate the safety and tolerability of fostamatinib administered orally for 24 weeks to subjects with IgA nephropathy.

3. Study Design

3.1 General Description

This is a Phase 2, multi-center, randomized, 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.
The study consists of 3 phases: a screening phase, a double-blinded treatment phase and a follow-up phase. Figure 1 presents the study design.

Figure 1: Study Design



Subjects who meet all inclusion/no exclusion criteria will be required to have completed at least 90 days of treatment with either an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) at the maximum approved (or tolerated) dose, and to have had a pre-study renal biopsy no more than 180 days prior to randomization (more than 180 days may be approved by the medical monitor on an individual basis). 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 randomization).

The enrollment plan for this study is to randomize patients in an ascending dose fashion. Once randomization of the initial cohort of 38 subjects (approximately 25 randomized to fostamatinib 100 mg bid, 13 to placebo) is complete, screening may begin for the second cohort of approximately 37 subjects (approximately 25 randomized to fostamatinib 150 mg bid, 12 to placebo). All subjects in Cohort 2 (150 mg bid or placebo) will be required to have proteinuria >1 gm/day (USA only) or > 0.5 gm/day (rest of the world) at Screening Visit 1b. Subjects will be randomized 2:1 in each cohort to maintain 1:1:1 allocation for all 3 double-blind dosing groups (25 subjects per group: see Table 1). Randomization 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 randomization (see Figure 1).

During the 24-week double-blind treatment period, subjects should remain on the same dose of angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) during the treatment period (Visits 2 – 9). Subjects will be monitored by routine safety assessments (vital signs, hematology, serum chemistries, urinalyses, and adverse event (AE) assessments) and for renal function. At the end of the treatment period, a renal biopsy will be obtained.

3.2 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 sPCR from Baseline to Week 24 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 and coefficient of variation of 0.923 at Baseline 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

Table 1 Study Treatment

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

3.3 Methods of Assigning Subjects to Treatment

An Interactive Web Response System (IWRS) will be used to randomize subjects to 1 of 2 groups in each cohort. The IWRS will assign numbered blister packs of study drug to each subject who is eligible for the double-blind treatment period of the study. Randomization will be stratified by the presence or absence of endocapillary hypercellularity at pre-study renal biopsy.

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. 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.

4. Study Endpoints and Covariates

4.1 Demographic and Baseline Characteristics

The demographics characteristics include: age, sex, race, height (cm), weight (kg), and body mass index (kg/m^2).

The baseline characteristics include: endocapillary hypercellularity (present vs absent), spot urine protein/creatinine ratio, mesangial hypercellularity score, estimated glomerular filtration rate.

4.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from Baseline of proteinuria, as measured by sPCR at Week 24.

4.3 Secondary Efficacy Endpoints

The following are the secondary efficacy endpoints considered for this study:

- Spot protein to creatinine ratio (sPCR):
  - Mean change from Baseline of sPCR at Week 12
  - Percentage of subjects with $\geq$ 30% reduction in sPCR from Baseline at Week 24
  - Percentage of subjects with $\geq$ 50% reduction in sPCR from Baseline at Week 24
  - Percentage of subjects with sPCR < 500 mg/g at Week 12
- Estimated glomerular filtration rate (eGFR):
  - Mean change from Baseline of eGFR ($mL/min/1.73\ m^2$) at Week 12
  - Mean change from Baseline of eGFR ($mL/min/1.73\ m^2$) at Week 24
- Haematuria (dipstick test):
  - Shift in haematuria (dipstick test) from baseline to Week 12
  - Shift in haematuria (dipstick test) from baseline to Week 24
- Biopsy Endpoints:
  - Mean change from pre-treatment to post-treatment in mesangial hypercellularity score (sum of mesangial scores/number of scoreable glomeruli) on renal biopsies
  - Shift in M Oxford Classification from pre-study renal biopsy to post-treatment renal biopsy
  - Mean change from pre-treatment to post-treatment in endocapillary hypercellularity score (sum of endocapillary scores/number of scoreable glomeruli) on renal biopsies
  - Shift in E Oxford Classification from pre-study renal biopsy to post-treatment renal biopsy

- Mean change from pre-treatment to post-treatment in cellular/fibrocellular crescent score (sum of cellular/fibrocellular crescent scores/number of scoreable glomeruli) on renal biopsies
- Mean change from pre-treatment to post-treatment in segmental sclerosis/adhesion score on renal biopsies (sum of segmental sclerosis/adhesion scores/number of scoreable glomeruli)
- Mean change from pre-treatment to post-treatment in global glomerulosclerosis score on renal biopsies (sum of global sclerosis scores/number of scoreable glomeruli)
- Mean change from pre-treatment to end of post-treatment in tubulointerstitial scarring on renal biopsies

4.4 Safety Endpoints

The following safety endpoints will be used to assess the safety and tolerability of fostamatinib:

- Incidence of adverse events
- Clinical laboratory results (hematology, serum chemistry, and urinalysis)
- Vital signs
- Physical examinations.

Safety parameters of interest will include increases in blood pressure, adverse effects on liver function tests including transaminase elevations, diarrhea, other GI symptoms and neutropenia.

4.5 Pharmacokinetic Endpoints

The pharmacokinetic endpoint of this study will be a preliminary assessment of the kinetics of fostamatinib in subjects with IgA nephropathy. Plasma concentrations of R406 will be obtained from samples collected at random during study visits (time from last dose will be collected for each sample).

4.6 Exploratory Immunohistochemistry Endpoints

Mean number of macrophages per scoreable glomerulus and the change from baseline will be summarized using descriptive statistics for both extra capillary CD68 macrophages and endocapillary CD68 macrophages.

Change from pre-treatment to post-treatment Syk, Phospho-Syk, Smad 6, and Smad 7 will be evaluated.

This immunohistochemistry analysis will occur once after all samples have been collected. Pathologists performing the analysis will remain blinded to individual treatment assignments until completion of the analysis.

5. Analysis Populations and Subgroup

5.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all randomized subjects. All efficacy endpoints will be analyzed using the ITT population. Subjects will be analyzed according to their randomized treatment assignment. The efficacy analyses in the ITT population will be considered the primary efficacy analyses.

5.2 Safety Population

The safety population will include all randomized subjects who received any amount of the allocated study drug. The safety population will be analyzed for all safety assessments. The subjects will be analyzed per the treatment they received.

5.3 Biopsy Population

The biopsy population will include all randomized subjects who receive at least 1 dose of allocated study drug and have both baseline and end of studies biopsies from at least 8 glomeruli. The biopsy population will be used for all biopsy analyses.

5.4 Pharmacokinetic Population

The pharmacokinetic population will include all randomized subjects who receive at least 1 dose of allocated study drug and have at least one plasma sample tested for R406. The PK population will be used for all PK analyses.

5.5 Treatment Groups for Analysis

For descriptive summaries, the following treatment groups will be used, unless otherwise indicated.

- Placebo (all placebo groups)
- 100 mg bid fostamatinib group
- 150 mg bid fostamatinib group
- Combined fostamatinib group

For comparisons of treatment differences in the analyses of efficacy endpoints, estimates of the following contrasts will be provided, unless otherwise indicated:

- Combined fostamatinib group vs placebo
- 150 mg bid fostamatinib group vs placebo
- 100 mg bid fostamatinib group vs placebo

For all the by-subject listings, the randomized treatment group will be presented.

5.6 Adjustments for Covariates

The randomization stratification factors and the baseline values of the response variables will be included in the statistical analysis model as covariates.

5.7 Multicenter Considerations

Study site will not be included as a factor in the statistical models

5.8 Multiplicity Considerations

No adjustments for multiplicity will be applied

6. Analytic Definitions

Age at Baseline is the last non-missing age collected before the first dose of study treatment.

Body Mass Index is calculated as (Weight in kg/(Height in meter)^2).The last non-missing weight and height collected before the first dose of study treatment will be used to calculate the baseline BMI.

Baseline Measurements will be the last measurement for the corresponding variable prior to the first randomized 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).

Study Day will be the number of days from first dose date of study drug for the assessments prior to the first dose date to assessment date. That is:

Study Day of post-dose assessment = Assessment Date – First Dose Date + 1.

Study Day of pre-dose assessment = Assessment Date- First Dose Date

Pre-treatment assessments could be up to 180 days prior to baseline. If there are more than two pre-treatment assessments for a subject, the last assessments will be used for the analyses related to 'pre-treatment'. Post-treatment assessments will be the assessments after the first dose of study drug. If there are more than two post-treatment assessments for a subject within an analysis visit, the last assessment that is closest to the scheduled study day will be used for the analyses related to 'post-treatment'.

Study Drug Exposure is calculated as number of days from first dose day to last. That is:

Study Drug Exposure = Last Study Drug Date – First Study Drug Date + 1.

Study Drug Compliance (%) for a subject is calculated as: 100*(total number of tablets dispensed during the double-blind treatment period – total number of tablets returned during the double-blind treatment period)/total number of tablets the subject was supposed to taken during the double-blind treatment period per protocol:

$$\text{Compliance (\%)} = 100 \times (\sum_{i=1}^{6} Di - \sum_{i=1}^{6} Ri) / \sum_{i=1}^{6} Ti * Pi$$

where:

i = study drug dispensation/return visit interval, i = 1 to 6

D_i = total number of tablets dispensed for visit interval i

R_i = total number of tablets returned for visit interval i

T_i = 2 for bid dosing and =1 for qd dosing, for visit interval i

P_i = total number of days in visit interval i.

The total number of tablets that were supposed to be taken during the double-blind treatment period excludes the number of tablets not taken due to a dose interruption. If a patient fails to return a study drug kit dispensed during the double-blind treatment period, then study drug compliance is considered to be missing.

Baseline sPCR: Two baseline sPCR value will be used in the analysis. In primary efficacy analysis, the baseline sPCR is defined as the average of non-missing value between Visit 2 and the most recent screening value prior to Visit 2. If only one non-missing sPCR is available, this value will be used as baseline.

A **Treatment-Emergent Adverse Event** (TEAE) is any adverse event that emerges on or after first dosing and prior to the end of follow-up (having been absent prior to treatment) or worsens relative to the pre-treatment state.

Hy's Law criteria are: concurrent aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN) with total (and/or direct/conjugated) bilirubin (TBL) > 2x ULN and alkaline phosphatase (ALP) < 2x ULN, and no other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, preexisting liver disease, or another drug capable of causing the observed injury.

Prior Medications will be defined as the medications used prior to the first dose of study drug. If the medication is used both prior to and on/after the first dose of study drug, the medication is both prior medication and concomitant medication.

Concomitant Medication will be defined as the medications used on/after the first dose of study drug.

7. Statistical Methods

The statistical analysis of the data obtained from this study will be performed using SAS® version 9.4 or higher. All inferential tests will be 2-sided and will be performed using a type I error rate of 5%, unless otherwise indicated.

Descriptive statistics for continuous variables will be presented with the, number of non-missing observations, mean, standard deviation, 25th percentile, median,75th percentile, minimum and maximum, unless otherwise specified. In general, the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD. If the raw data have 3 decimals or more, 3 decimals will be presented for mean, median, minimum and maximum, and SD.

For categorical data, descriptive statistics will be presented with the number and percentage of subjects in the various categories of the endpoint. One decimal will be presented for percentages. Percentages equal to 100 will be presented as 100%.

All data collected in clinical database will be listed in by-subject listings for subjects in the ITT population (i.e. the randomized subjects), unless otherwise indicated.

7.1 Subject Disposition and Protocol Deviations

Subject disposition will be summarized by treatment as number of screened subjects, randomized subjects, the number and percentage of subjects in each analysis population, and the number and percentage of subjects who complete the study or withdraw (the latter summarized by reason for withdrawal).

Subject disposition will also be summarized by Site ID. This summary will include the number of subjects treated, completed and discontinued early by each part of the study.

Major protocol deviations collected on case report forms will be tabulated by treatment and the deviation category (Enrollment Criteria, Non-Compliance, Laboratory, Dosing, Visit Schedule, Visit/Procedure Requirement, Concomitant Medication, Regulatory, and Other) in the ITT population. The final protocol deviation (i.e., unplanned deviation) and protocol exemption (i.e., planned deviation) data will be reported in the Listing outputs.

7.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment in the ITT population.

Medical history will be coded using the Medical Dictionary for Regulatory Affairs (MedDRA), using the latest version available at the time of the interim analysis, as specified in the Data Management Plan (DMP). The medical history conditions will be summarized by treatment, system organ class and preferred term in the ITT population.

Prior IgA Nephropathy and Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DDE) available at the time of the IA, as specified in the DMP. Prior and concomitant medications will be summarized by treatment,

anatomical therapeutic chemical classification (ATC) level 2 term and preferred term in the ITT population. Additionally, the number and percentage of Subjects who changed anti-hypertensive regimen during the treatment period, either in medication or dose of medication, will be summarized by study stage and listed. Anti-hypertensive medications are medications with the following ATC codes:

- CO2: Anti-hypertensives
- CO3: Diuretics
- CO4 Peripheral Vasodilators
- CO7: Beta blocking agents
- CO9: Agents acting on the renin-angiotensin system.

7.3 Treatment Exposure and Compliance

Study drug exposure and compliance will be summarized descriptively by treatment in the safety population.

Study drug compliance will be calculated only for the 24-week main study treatment period and not for the extension period.

7.4 Analysis of Primary Efficacy Endpoint

The primary efficacy endpoint is the mean change from Baseline of proteinuria, as measured by sPCR at Week 24. The sPCR will be $\log_{10}$-transformed prior to analyses.

7.4.1 Main Analysis

The primary efficacy endpoint will be analyzed using an analysis of covariance (ANCOVA) model based on the ITT population. The ANCOVA model will include both the treatment groups and the presence/absence of endothelial hypercellularity at baseline as factors and adjust for the sPCR at baseline (as a covariate). If required and when possible, missing Week 24 data will be imputed using an appropriate Multiple Imputation (MI) procedure. Should Multiple Imputation procedures fail, last observation carried forward (LOCF) will be used as an alternative imputation algorithm.

The regression method for monotone missing data (SAS PROC MI) will be used for multiple imputation. For patients who discontinued the study due to adverse events, consider the missing data mechanism for the missing change from baseline values to be missing not at random (MNAR). For patients who discontinued the study due to reasons other than adverse events or patients who completed the study but have missing data at a visit, consider the missing data mechanism for the missing change from baseline values to be missing at random (MAR).

Missing data will be imputed in two separate subgroups. The first subgroup will contain all patients randomized to a Fostamatinib group that have data available at the visit or have a MAR missing data mechanism. The second subgroup will contain all patients randomized to placebo as well as fostamatinib patients missing data at the visit with an MNAR missing data mechanism.

Multiple imputation will then be performed within each subgroup, resulting in missing data for Fostamatinib patients under an MAR missing data mechanism imputed from a model obtained only from Fostamatinib treated patients, and missing data from all placebo patients as well as Fostamatinib treated patients with an MNAR missing data mechanism imputed from a model obtained only from placebo treated patients. After obtaining complete data sets for both subgroups, the complete data sets after combining subgroups will be used in the analysis, and inferences from each complete dataset will be combined to obtain an overall test statistic.

7.4.2 Sensitivity Analyses

While the inferential analysis methodology will remain unchanged for sensitivity analyses of the primary endpoint, one method of imputing missing data will be performed before inferential analysis:

The LOCF procedure in the ITT population – This analysis will use an ANCOVA model. The ANCOVA model will include both the treatment group and the presence/absence of endothelial hypercellularity at baseline as factors and adjust for the sPCR at baseline (as a covariate). Dependent variable is change from baseline to Week 24 in sPCR. Missing Week 24 data will be imputed using the LOCF procedure. Pre-treatment values will not be carried forward.

7.4.3 Subgroup Analysis

Sample size permitting, the primary efficacy analysis will also be conducted for the following subgroups:

1. Time since initial exposure to RAS blockade (< 6 months vs ≥ 6 months from baseline). The initial exposure to RAS blockade (angiotensin II receptor blocker (ARB) or angiotensin converting enzyme inhibitor (ACEI)) will be derived from prior/concomitant medication collected on CRF. The imputed medication start date will be used to calculate the duration of the exposure from baseline.

2. Baseline sPCR: sPCR > 2000 mg/g and sPCR > 3500 mg/g.

7.4.4 Analysis by Geographic Regions

Due to the small sample size, no analysis by geographic region is planned

7.5 Analysis of Secondary Efficacy Endpoints

All secondary efficacy endpoints will be analyzed using the ITT population except for biopsy endpoints that will be analyzed using the Biopsy Population.

Continuous secondary endpoints will be analyzed using an ANCOVA model which includes the treatment and presence/absence of endothelial hypercellularity at baseline as factors and adjusted

for the baseline value. The LS mean differences between treatment groups (combined fostamatinib group vs placebo; 150 mg fostamatinib group vs placebo; 100 mg fostamatinib group vs placebo separately) accompanied by 95% confidence interval and the p-value for testing the treatment difference will be presented.

Shift tables will display the change in category from pre-study renal biopsy to post-treatment renal biopsy for each of the components of the Oxford Classification scoring:

- Mesangial hypercellularity (M_0 is $\leq 50\%$ of glomeruli show mesangial hypercellularity; M_1 is $> 50\%$ of glomeruli showing mesangial hypercellularity)
- Endocapillary hypocellularity (E_0 is no endocapillary hypercellularity; E_1 is any glomeruli showing endocapillary hypercellularity)
- Segmental glomerulosclerosis (S_0 = absent; S_1 present in any glomeruli)
- Tubular atrophy/interstitial fibrosis (T_0 is $0 - 25\%$ of cortical area shows tubular atrophy or interstitial fibrosis; T_1 is $26 - 50\%$; T_2 is $> 50\%$)

Cochran–Mantel–Haenszel (CMH) test will assess whether there is an association between the change in these categories from pre-treatment to post-treatment and treatment group (combined fostamatinib group vs placebo; 150 mg fostamatinib group vs placebo; 100 mg fostamatinib group vs placebo separately) while controlling for the presence/absence of endothelial hypercellularity at baseline.

Missing data for the secondary endpoints will not be imputed.

7.6 Analysis of Safety Endpoints

Safety data will be summarized descriptively. No inferential statistics will be provided. All safety analyses and summaries will be based on the safety population.

7.6.1 Adverse Events

Adverse events (AEs) will be coded using the World Health Organization Drug Dictionary (WHO-DDE), version as defined in the DMP.

Incidence for the following treatment-emergent adverse events will be summarized by system organ class, preferred term and treatment based on the safety analysis set. Subjects are counted only once within each system organ class and each preferred term.

- All TEAEs
- All TEAEs by fostamatinib dose at onset
- All TEAEs by maximum severity in the following order: severe, moderate and mild (if severity is missing, the AE will be considered as severe for summary tables and will be presented in the data listing with a missing severity)

- All TEAEs by strongest relationship to study drug in the following order: probable, possible and unlikely (the relationship to study drug will be determined by investigators). If causality is missing, the adverse event will be considered probable for summary tables but will be presented in the data listing with a missing relationship.
- Serious TEAEs
- Serious TEAEs by fostamatinib dose at onset
- TEAEs leading to discontinuation of study treatment
- TEAEs leading to discontinuation of study treatment by fostamatinib dose at onset
- TEAEs of special interest (AESI) (including—but not limited to--increases in ALT, AST, and/or total bilirubin, absolute neutrophil counts (ANC) < 1000/mm3 or 1.0 x 109/L, severe diarrhea, hypertension uncontrolled by oral antihypertensive medications that recorded in dose adjustment)
- TEAEs of special interest by fostamatinib dose at onset

All AEs, serious AEs, deaths, AEs leading to discontinuation of study drug, and AEs of special interest will be listed in by-subject listings separately.

7.6.2 Clinical Laboratory Evaluations

Actual values and the change from baseline to each scheduled visit in hematology, serum chemistry, and quantitative urinalysis test results will be summarized by dose. Actual values of categorical urinalysis test results will be summarized by dose and scheduled visit.

Shift tables will be used to summarize laboratory tests. Normal ranges for each parameter in hematology and serum chemistry will be used to categorize the test results as low (value lower than the lower limit of normal [LLN]), normal (value within the normal range), or high (value higher than the upper limit of normal [ULN]).

Additionally, number and percentage of subjects with elevated transaminase tests or who meet Hy's law criteria during the post-baseline (defined as the assessments after the first dose of study drug) will be summarized by study stage. All test results for AST, ALT, total bilirubin and alkaline phosphatase for the subjects who meet Hy's law criteria will be listed in a by-subject listing.

No analysis of urinalysis tests is planned for this study.

7.6.3 Vital Signs

Actual values and the change from baseline to each scheduled visit for each vital sign parameter will be summarized by dose and scheduled visit.

The frequency of systolic and diastolic blood pressure abnormalities based on the:

- Highest-post treatment value
- Last post-treatment evaluation

will be summarized in shift tables. Blood pressure abnormalities are described in Appendix C.

7.6.4 Physical Examinations

The results of physical examinations will be presented only in a by-subject listing

7.7 Analysis of Pharmacokinetic Endpoints

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

7.8 Analysis of Immunohistochemistry Endpoints

The observed number of macrophages per glomerulus and the change from baseline will be summarized using descriptive statistics by treatment for both extra capillary CD68 macrophages and endocapillary CD68 macrophages.

Change from pre-treatment to post-treatment Syk, Phospho-Syk, Smad 6, and Smad 7 will be evaluated. Other parameters to be included in the analyses will be determined after database lock.

Additionally, the mean number of macrophages per scorable glomerulus and phospho-Syk staining at Baseline will be correlated with change from baseline in sPCR at Week 24.

8. Interim Analysis

An interim analysis of topline safety and efficacy data will be conducted after all of the patients in Cohort 1 have completed their Week 26 follow-up visit. The interim analysis will be performed on the ITT population, but the primary endpoint will only include subjects that completed dosing through Week 24.

The data from all of the Cohort 1 patients will be cleaned and then all Cohort 1 patient data will be hard-locked prior to the interim analysis. A review of all protocol deviations will be performed prior to the hard-lock for the interim analysis and all Cohort 1 patients will be assigned to the various analysis populations before unblinding occurs for the interim analysis. These procedures are intended to minimize potential bias when the final efficacy and safety analyses are performed at the completion of the trial.

Results from the interim analysis will not be used decide whether to stop or continue the trial based on the efficacy of the 100 mg bid fostamatinib arm. The study's statistical power is expected to be too low mid-way through the trial to make such decisions. Instead, results from the interim analysis will be used to guide business decisions about the further development of fostamatinib for this particular indication.

The interim analysis will summarize the following efficacy and safety results by treatment group:

- Subject disposition
- Demographic and baseline data
- The change in sPCR from baseline by visit
- Summary of sPCR 30% responders by visit
- Summary of sPCR 50% responders by visit
- Summary of sPCR 50% responders at week 24 by visit
- Histologic changes of pre- vs. post-treatment renal biopsies
    - Mesangial hypercellularity score
    - Endocapillary hypercellularity score
    - Segmental sclerosis/adhesion score
    - Global glomerulosclerosis score
    - Tubulointerstitial scarring (interstial fibrosis/tubular atrophy) score
- Frequency of AEs and SAEs by SOC and PT
- Change from baseline in eGFR (mL/min/1.73 m^2) at Weeks 12 and 24
- Summary of ALT, AST and total bilirubin abnormalities based on maximum values
- Summary of ALT, AST, and serum creatinine by visit
- Summary of vital signs by visit

Only descriptive statistics for efficacy (and safety) data will be provided at the interim analysis. No inferential statistical analyses will be performed on the efficacy data. Additionally, no imputation will be done for missing data in the interim analysis; only observed data will be reported. Consequently, no adjustment for alpha spending will be made at the completion of the trial.

Listings of the data identified above will also be provided for the Cohort 1 subjects at the interim analysis.

9. Safety Review Committee

Because fostamatinib has been widely used in other treatment settings and its safety profile is well-known, no new safety issues were expected to be identified by this small study. However, because subjects are being treated in a new indication and at higher doses of fostamatinib than used in the large rheumatoid arthritis program from which the majority of prior safety information was collected, an unblinded Safety Review Committee (SRC) was established to periodically monitoring the emerging safety data from the trial. The composition, roles, and responsibilities of the SRC have been defined in a separate SRC charter document.

10. Visit Windows

Assessments will be reassigned to the scheduled visits according to the following visit windows. If there are multiple assessments assigned to the same visit window after the early termination visit reassignment, the non-missing value closest to the scheduled study day will be used. If there

are multiple assessments with non-missing values with the same number of days from the scheduled study day, the latest one will be used.

Table 5: Analysis Visit Window

Scheduled Visit	Study Day	Visit Window (Study Day)
Week 1	7	2 - 10
Week 2	14	11 – 21
Week 4	28	22 – 42
Week 8	56	43 – 70
Week 12	84	71 – 105
Week 18	126	106 – 147
Week 24	168	148 – 180
Week 26	182	181 or Later Not in Extended Treatment

11. Handling of Missing Data

11.1 Missing Efficacy Data

Missing Week 24 values of sPCR will be imputed using a multiple imputation (MI) procedure for the primary analysis of primary efficacy endpoint and using a last observation carried forward (LOCF) as sensitivity analysis. The details of imputation methods are described in the analysis of efficacy section.

Missing data for the secondary endpoints will not be imputed.

11.2 Adverse Events Missing Data

Treatment-emergent adverse events (TEAEs) with missing severity will be considered severe and TEAEs with missing relationship will be counted as related.

In cases where the start date is not complete, the assumption will be made that the adverse event is a treatment-emergent event unless there is evidence to the contrary. The first treatment start date will be used as the AE start date if the start date is missing. Missing AE end date will not be imputed. The AE will be assumed as ongoing if end date is missing.

11.3 Concomitant Medications Missing Dates

In cases where the start or stop dates are not complete, the assumption will be made that the medication is a concomitant medication unless there is evidence to the contrary.

If year and month of the dates are available (and only day is missing) the first day of the month will be used to impute start date, and the last day of the month will be used to impute stop date.

If only the year is available and it is before the year of first study treatment date, January will be used to impute the start date and December will be used to impute the stop date. If the year is equal to the year of the first study treatment date, month and day of the first study treatment date

will be used to impute the start date, and month of the last study treatment date will be used to impute the stop date.

If the start or stop date is completely missing, use the first study treatment date to impute the start date, and the last study treatment date to impute the stop date.

Imputed dates will be used for categorization of medications to concomitant or prior, but data listings will present the date as recorded on the CRF.

12. REFERENCE

1. Little, R.J.A. and Rubin, D.B. (1987), Statistical Analysis with Missing Data, New York: John Wiley & Sons, Inc

2. Yang C. Yuan, Multiple Imputation for Missing Data: Concepts and New Development, P267-25, SAS Institute Inc., Rockville, MD

13. Appendices

A. Error! Reference source not found. **Timeline**

Main Study (Visit 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		

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* ***Error! Reference source not found.***.

[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* ***Error! Reference source not found.****.*

[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.*

B. Laboratory Test

Normal ranges for each parameter in hematology and serum chemistry will be used to categorize the test results as low (value lower than the lower limit of normal [LLN]), normal (value within the normal range), or high (value higher than the upper limit of normal [ULN]).

The table below provides the normal values for urinalysis tests. Any values other those listed will be considered "abnormal" for the purpose of shift tables presentation.

Urine Dipstick Test Name	Normal Reference Range	
	Low	High
Appearance	Clear	Clear
bilirubin	Negative	Negative
Blood	Negative	Negative
Glucose	Negative	Negative
Ketones	Negative	Negative
Leukocyte Esterase	Negative	Negative
Nitrite	Negative	Negative
pH	5	8
Protein	Negative	Negative
Specific Gravity	1.001	1.035
Urobilinogen	Normal	Normal
Urine Microscopy	Normal	Normal

C. Error! Reference source not found. **Pressure**

The 2017 ACC/AHA guidelines will be followed for the analysis of blood pressure data. The following classification will be followed:

Systolic and Diastolic Blood Pressure Abnormalities

	Upper Limit of Blood Pressure (mm Hg)		
Classification	**Systolic**		**Diastolic**
Normal	less than 120	and	Less than 80
Elevated	120 – 129	and	Less than 80
Stage 1	130 – 139	or	80 – 89
Stage 2	140 or Higher	or	90 or Higher
Hypertensive Crisis	Higher than 180	or	Higher than 120

If a subject's blood pressure satisfies more than one classification, the more severe classification will be assigned. Classifications above are ordered in from less sever to most severe.

For the purpose of analysis of shift in vital signs will be considered normal according to the following cut offs:

Vital Sign Normal Ranges

Vital Sign	**Normal Range**
Systolic/Diastolic blood pressure	Less than 120/80 mm Hg
Heart rate	50 – 100 beats/min

D. Assessment of Renal Biopsies

The following data will be obtained for each biopsy:

- 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 6):

- 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.

Table 6: Oxford Classification of Renal Biopsy Scoring

Variable	Definition	Score
Mesangial hypercellularity	<4 Mesangial cells/mesangial area=0	M0
	4–5 Mesangial cells/mesangial area=1 6–7 Mesangial cells/mesangial area=2 ≥ 8 Mesangial cells/mesangial area=3	M1
	The mesangial hypercellularity score is the mean score for all glomeruli	
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%

E. Example SAS Code of Multiple Imputation

Step 1: Impute non-monotone missing visits using MCMC

```
proc mi data=TEMP seed=007 nimpute=10 out=OUTMI_1;
  mcmc impute=monotone chain=multiple;
  var trt1 trt2 endohbl base visit3--visit9;
run;
```

Step 2a: Impute monotone missing visit using a monotone regression model for non-placebo subjects who discontinued for reasons other than AE

```
proc mi data=OUTMI_1 seed=007 nimpute=1 out=OUTMI_2A;
  where trt01pn>1 & comp24wk^='ADVERSE EVENT';
  class trt01pn endohbl;
  monotone reg(visit9);
  var trt01pn endohbl base visit3--visit9;
run;
```

Step 2b: Impute monotone missing visit using a monotone regression model for placebo subjects or non-placebo subjects who discontinued due AE

```
proc mi data=OUTMI_1 seed=007 nimpute=1 out=OUTMI_2B;
  where trt01pn=1 or (trt01pn>1 & comp24wk='ADVERSE EVENT');
  class endohbl;
  monotone reg(visit9);
  var endohbl base visit3--visit9;
run;
```