FibroGen, Inc.

An Open-Label Extension Study to Evaluate the Efficacy and Safety of FG-4592 for the Long-Term Maintenance Treatment of Anemia in Dialysis and Non-Dialysis Patients with Chronic Kidney Disease

FGCL-4592-059

STATISTICAL ANALYSIS PLAN

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Approvals

I have reviewed and accept the information in this document to be a true and accurate representation of the Statistical Analysis Plan for Study FGCL-4592-059.

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Signature Significance

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Signature	Significance
Initiator	By signing, the author is attesting that the content of the document is complete and accurate.
Reviewer	By signing, the reviewer is attesting that the document's approach and contents are compliant with the study protocol, all appropriate, regulatory requirements, and other significant guidelines. This individual(s) has reviewed the document for accuracy and completeness.

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LIST OF ABBREVIATIONS

AE	Adverse Event
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ESA	Erythropoiesis-Stimulating Agent
FACT-An	Functional Assessment of Cancer Therapy – Anemia
Hb	Hemoglobin
HDL	High-Density Lipoprotein
IV	Intravenous
LDL	Low-Density Lipoprotein
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Potentially Clinically Significant
PEY	Patient-Exposure-Year
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment Emergent Adverse Event
TIBC	Total Iron Binding Capacity
TLF	Tables, Listings, and Figures
TSAT	Transferrin Saturation
UACR	Urine Albumin-to-Creatinine Ratio
ULN	Upper Limit of Normal, value provided by the laboratory

WHODD	World Health Organization Drug Dictionary
WHO	World Health Organization
SOC	System Organ Class (used in MedDRA dictionary)

1 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of efficacy and safety as outlined and/or specified in the final study protocol. Specifications of tables, data listings, and figures (TLF) are contained in a separate document.

2 STUDY OBJECTIVES

The primary objectives of this study are to:

- Evaluate the long-term efficacy and safety of roxadustat in the maintenance of Hb in dialysis and non-dialysis CKD subjects.

The secondary objectives in this study are to:

- Evaluate roxadustat doses and dose adjustments.

The exploratory objectives in this study are to:

- Assess the effect of roxadustat on iron utilization parameters;
- Assess the effect of roxadustat on select biomarkers.

3 STUDY DESIGN

This is an open-label, long-term maintenance study of roxadustat anemia therapy in dialysis and non-dialysis subjects with CKD who completed the treatment period of a Phase 2 roxadustat anemia study in the U.S.

Subjects who received roxadustat in a previous study continued to receive roxadustat at the same dose and frequency as they received at the end of the treatment period in their previous study, unless a dose adjustment was required, at time of switching over to this study. Roxadustat was supplied in an open-label manner to all subjects.

This study (amendment 2) accommodated the potential for prior study participants on a placebo, to switch to this study: Subjects who received placebo in their previous study could start treatment with roxadustat at starting doses according to their weight (Appendix B of the protocol). Planned total study duration was up to 312 weeks (6 years), including up to an additional 1 year under Amendment 2.

Study visits were scheduled every 2 weeks, for the first 104 weeks (2 years) of study drug treatment (time on the previous Phase 2 studies of roxadustat), followed by every 4 weeks until the end of the treatment period.

After the end of treatment (defined as the last day a subject receives study drug) the subjects returned for a follow-up visit 4 weeks later.

The baseline Hb value for efficacy analysis is defined as the mean of the central laboratory Hb value from the baseline visit at Day 1 (prior to receiving the first dose of study drug in this study), plus any other central lab Hb values within 15 days prior to Day 1.

Safety is assessed by vital signs, physical examinations, clinical laboratory values (serum chemistries including liver function tests [LFTs] and complete blood counts [CBC]), electrocardiograms (ECGs), AEs and concomitant medication reporting. Clinical laboratory tests, including LFTs and Hb levels, could y be assessed at additional times on unscheduled visits for safety reasons.

Fifteen subjects entered this study: 1 subject from FGCL-4592-040 and 14 subjects from FGCL-4592-041. All subjects received Roxadustat prior to entering this study (0 subject received placebo). Descriptive analyses will be performed for all subjects.

4 STUDY ENDPOINTS AND ASSESSMENTS

4.1 EFFICACY ENDPOINT

The efficacy endpoints in this study are:

- Mean Hb over selected time periods
- Number (%) of subjects maintaining mean Hb at ≥10 g/dL at selected time periods
- Rescue therapy events (composite of transfusions, IV iron, ESAs) and individual rescue therapy modalities
- Roxadustat average weekly doses over selected time periods
- Dose adjustment frequencies (increase, decrease, dose hold, separately)
- Oral iron dose

4.2 SAFETY ASSESSMENTS

Safety assessments include the following:

- Number (%) of subjects with AEs, serious adverse events (SAEs), and clinically significant changes in laboratory values from baseline observations
- Changes from baseline observations in vital signs and ECG findings, and clinical laboratory values, including Total Cholesterol, LDL cholesterol, LDL/HDL ratio, non-HDL cholesterol, HDL cholesterol TSAT, and Ferritin

4.3 SELECT ADDITIONAL LABS OF INTEREST

Exploratory assessments in this study will evaluate the following parameters:

- Reticulocyte hemoglobin content (CHr)
- Highly sensitive C-reactive protein (hs-CRP)
- Hepcidin levels in serum
- eGFR

5 GENERAL STATISTICAL CONSIDERATIONS

5.1 SAMPLE SIZE DETERMINATION

This is an open-label, long-term maintenance study of roxadustat anemia therapy in dialysis and non-dialysis CKD subjects who have completed the treatment period of a phase 2 roxadustat anemia study in the U.S. The study allowed up to 50 non-dialysis, HD, and PD subjects, from up to 20 study centers throughout the U.S.

No power analysis was used to determine the sample size. Analysis Populations

All subjects entered into this study are included for the statistical analyses.

5.2 METHODOLOGY AND CONVENTIONS

Descriptive summary statistics as well as 95% CI for the estimate, if applicable, are provided.

Continuous variables are presented by descriptive statistics: n, mean, standard deviation, median, 25^{th} and 75^{th} percentile, minimum, and maximum. Categorical variables are presented by frequency count and percentage.

Lab results obtained from a central laboratory were used for all analyses. Local laboratory values, if collected in the CRF's, were not recorded.

All confidence intervals are two-sided 95% confidence intervals. All analyses performed use SAS® Version 9.3 or higher.

5.3 ADDITIONAL DATA HANDLING RULES AND PRESENTATION SPECIFICATIONS

The following general guidelines apply to all statistical analyses and data presentations:

- The baseline Hb value for efficacy analysis is defined as the mean of the central laboratory Hb value from the baseline visit at Day 1 (prior to receiving the first dose of study drug in this study), plus any other central lab Hb values within 15 days prior to Day 1
- Baseline of other assessments is defined as the last available value obtained prior to the first dose of study drug in this study, unless otherwise specified in this SAP.
- Analysis visits (instead of the nominal visits from CRF) derived from visit dates and visit time windows are used in all analyses, tables, listings and figures. Unscheduled visits within an allowable window are grouped into the closest scheduled visits based on the visit window specified in Appendix 1. For subjects who have more than one measurement at a scheduled visit, the last measurement issued, with the exception of CPK, WBC, liver function tests (i.e., ALT, AST, GGT, ALP, and total bilirubin), in which the maximum measurement issued.
- By default, US conventional units are used for laboratory value presentations. A set of lab summary tables in SI units are also provided based on TLF index.
- Age is calculated as of date that the informed consent form was signed.

  - age = INTCK('YEAR', Birth Date, Date of Informed Consent, 'C')
  where INTCK is a SAS function.

- Body weight, height and temperatures are converted using the following formula:

  - kg = lb/2.2
  - cm = 2.54 x in
  - $C^o = (5/9) \times (F^o - 32)$

- For continuous variables that are recorded as "<X" or ">X", the value of "X" issued in the calculation of summary statistics.
- The mean, standard deviation and median is presented with adding one more decimal to raw data with rounding off. The minimum and maximum is presented with the same number of decimals as in the raw data.
- All percentages are rounded to one decimal place and lined up by the decimal place. The percentage is suppressed when the count is zero.
- Any p-values are rounded to four decimal places and presented as '<.0001' if they are less than 0.0001before rounding.
- All tables and listings have a header showing "FibroGen, Inc.", the protocol number, date of the database transfer, and Page x of y. A footer shows the program file path/name, output file path/name, run date and run time.
- Additional data handling conventions are detailed in Appendix 1.

6 SUBJECT ACCOUNTABILITY AND DISPOSITION

Number and percent of subjects are summarized by discontinuation reason.

7 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters and important baseline and disease characteristics are summarized. These include but may not be limited to age and age group, sex, ethnicity, race, weight, body-mass index (BMI), Hemoglobin, Ferritin and Ferritin group (<=100 vs. >100 ng/mL), TSAT and TSAT group (<=20% vs. >20%), iron repletion status ([TSAT $\geq$20% and ferritin $\geq$100 ng/mL] vs. other), baseline C-reactive protein (CRP) group (CRP $\leq$ULN vs. CRP > ULN), eGFR and eGFR group (<10, 10-<15, 15-<30, 30-<45, 45-<60, and >=60 mL/min/1.73m^2).

8 STUDY MEDICATION

8.1 EXTENT OF EXPOSURE AND DOSE ADMINISTRATION

Treatment duration, the Patient-Exposure-Year (PEY) are defined as (Last Dose Date – First Dose Date + 1)/365.25, during this study.

Average weekly study dose (in mg or mg/kg) are summarized for selected time periods such as every 4 weeks, from week 0 – 24, every 8 weeks, from week 25-48, and every 12 weeks, starting week 49 through EOT/ET.

Dose adjustment frequencies (number (%) of subjects with a dose increase, dose decrease, dose hold, separately)

8.2 TREATMENT COMPLIANCE

Study medication compliance for a specified period is defined as the total dose (mg) actually taken by a patient during that period divided by the prescribed dose expected to be taken during the same period multiplied by 100. Descriptive statistics for study medication compliance is presented.

9 CONCOMITANT MEDICATIONS

The World Health Organization Drug Dictionary (WHODD) Version 15 isused to classify concomitant medications by therapeutic class and preferred term based on ATC code level 3. Concomitant medication is defined as any medication taken between the day of first dose of the study medication and the day of last study medication date. For this study, all medication reported are considered as concomitant medication.

Concomitant medication usage is summarized by the number and proportion of subjects receiving each medication within each therapeutic class using the safety population. Multiple drug usage by a patient is counted only once.

10 EFFICACY ANALYSES

Descriptive analyses will be performed for all subjects.

10.1 ANALYSES OF EFFICACY ENDPOINTS

The following efficacy endpoints based on the observed data will be summarized at the analysis visits in Section 13.1:

- Mean Hb values over selected time ; mean Hb overlay mean weekly roxadustate dose over time plot.
- Number (%) of subjects with mean Hb at ≥10 g/dL averaged over selected time periods
- Number of rescue therapy events (composite of transfusions, IV iron, ESAs) of total PEY (defined as the sum of all subject's individual PEY) and number of individual rescue therapy modalities of total PEY (this can be expressed as per 100 PEY dependent on the magnitude of the result). PEY is defined as (last dose date – first dose date+1)/365.25
- Mean monthly oral iron dose (note the monthly dose is defined as sum of weekly dose over 4 weeks) at specific time periods
- Mean Reticulocyte hemoglobin content (CHr) at selected time points
- Mean Highly sensitive C-reactive protein (hs-CRP) at selected time points
- Mean Hepcidin levels in serum at selected time points
- Mean eGFR at selected time points
- Mean Total Cholesterol, LDL cholesterol, LDL/HDL ratio, HDL cholesterol, non-HDL cholesterol at selected time points

- Mean TSAT and Ferritin at selected time points

11 SAFETY ANALYSES

11.1 ADVERSE EVENTS

An AE (classified by preferred term) occurring after the first dose of study medication and up to the last dose of study medication +28 days is considered a treatment emergent adverse event (TEAE) if it was not present prior to the first dose of study medication, or it was present prior to the first dose of study medication but increased in severity during the treatment period.

The number and percentage of subjects reporting TEAEs are tabulated by system organ class and preferred term. If more than one event occurs with the same preferred term for the same patient, the patient is counted only once for that preferred term using the most severe and most relatedness occurrence for the summarization by severity and by relationship to the study medication. In addition to the frequency tables above, crude event rate are provided. The crude event rate of interest (per 100 patient exposure years) by system organ class and preferred term is calculated as: number of the events per PT and SOC / total patient exposure years (PEY)*100.

The following TEAE table and listings are provided.

1. TEAE by system organ class and preferred term
2. TEAE by system organ class, preferred term, and maximum severity
3. TEAE by system organ class, preferred term, and relationship to study medication
4. Treatment-emergent serious AEs (TESAE) by system organ class and preferred term
5. TEAEs leading to discontinuation of study medication or from the study will be summarized by preferred term and treatment group
6. Listing of subjects with serious adverse events (SAEs)
7. Listing of subjects with adverse events leading to discontinuation of study medication or from the study

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for the following laboratory values and changes from baseline at selected time points are presented to include (but not limited) to the following:

Hematology: Hemoglobin, hematocrit, RBC count, CHr, MCV, WBC count, WBC differential, and platelet counts;

Chemistry: Alkaline phosphatase, ALT, AST, total bilirubin, TSAT, ferritin, total cholesterol, LDL cholesterol, HDL cholesterol, LDL/HDL ratio, CPK, LDH, total protein, albumin, fasting glucose, phosphate, uric acid, BUN, creatinine, sodium, and potassium; HbA1C;

11.3 VITAL SIGNS

Blood Pressures and Heart Rate baselines are defined as the mean of values obtained from the last 2 weeks of screening including Day 1 prior to the first dose.

Descriptive statistics are provided for vital signs (e.g., systolic and diastolic blood pressure, MAP, pulse rate, and respiratory rate) and their changes from baseline at each visit and at the end of study.

11.4 ELECTROCARDIOGRAM (ECG)

Descriptive statistics are provided for ECG parameters (e.g., Heart Rate, PR interval, QRS interval, QT interval, and QTc interval) at baseline and changes from baseline at each assessment time point. QTc interval is calculated using both Bazett ($QTcB = QT/(RR)^{1/2}$) and Fridericia ($QTcF = QT/(RR)^{1/3}$) corrections; and if RR is not available, it is replaced with 60/HR in the correction formula.

12 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 8. General Considerations of Clinical Trials, July 1997. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

13 APPENDIX 1: DATA HANDLING CONVENTIONS

13.1 VISIT TIME WINDOWS

Endpoint	Visits during Treatment Period				
	Every 4 weeks [a]	**Every 24 weeks [b]**	**Target Day**	**Analysis Visit Windows Actual Assessment Day[+]**	**Analysis Visit++**
			Day 1	Day 1	Baseline
BP, HR, respiratory rate*	X		Day 7 * (Week #) + 1	Target Day plus or minus half the duration to the next Target Day	Weeks 4, 8, 12 then every 12 weeks
12-lead ECG		X	Day 7 * (Week #) + 1	[Target Day – 84, Target Day + 83]	Week 24, 48, …
Hb, reticulocyte count, CHr*	X		Day 7 * (Week #) + 1	Target Day plus or minus half the duration to the next Target Day	Weeks 4, 8, 12 then every 12 weeks
CBC with WBC differential *	X		Day 7 * (Week #) + 1	Target Day plus or minus half the duration to the next Target Day	Weeks 4, 8, 12 then every 12 weeks
Fasting serum chemistry (including LFTs, lipid panel, glucose)	X		Day 7 * (Week #) + 1	Target Day plus or minus half the duration to the next Target Day	Weeks 4, 8, 12 then every 12 weeks
Serum iron, ferritin, transferrin (or TIBC), TSAT	X		Day 7 * (Week #) + 1	Target Day plus or minus half the duration to the next Target Day	Weeks 4, 8, 12 then every 12 weeks
Special labs (CHr, hepcidin, hs-CRP, plus exploratory biomarkers)[l]		X	Day 7 * (Week #) + 1	[Target Day – 42, Target Day + 41]	Week 24, 48, …

Abbreviations: BP = blood pressure; CBC = complete blood count; CHr = reticulocyte hemoglobin content; CRP = C-reactive protein; ECG = electrocardiogram; HR = heart rate; LFT = liver function test; TIBC = total iron binding capacity; TSAT = transferrin saturation; WBC = white blood cell.

***** Visit weeks are weekly (week 1 to 4), every 2 weeks (week 6 to 24), every 4 weeks afterwards

a Visit weeks may include of: Weeks 13, 37, 61, 85, 109, 133, 157, 181, 205, 229, and 253

b Visit weeks may include of: Weeks 25, 49, 73, 97, 121, 145, 169, 193, 217 and 241

++ Analysis visits are up to the EOT, which is the last day of treatment.

Note: The lower bound for the first visit window starts at Day 1.

13.2 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments prior to switch to this study, the last result prior to switch is used as baseline, except where otherwise specified. If post-baseline assessments are repeated or unscheduled, the last post-baseline assessment within a visit window is used as the study visit assessment for generating summary statistics. However, all post-baseline assessments are used for PCS value determination and all assessments are presented in the data listings.

13.3 MISSING DATE OF STUDY MEDICATION

When the last study drug administration date is missing, all efforts should be made to obtain the date from the investigator. If it is still missing after all efforts, then the last recorded visit date during the treatment period is used in the calculation of treatment duration.

13.4 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE started prior to the study medication, then a severity of "Mild" is assigned. If the severity is missing for an AE started on or after switch to this study then a severity of "Severe" is assigned. Imputed values for severity assessment are used for incidence summary, while the actual missing values are presented in data listings.

13.5 MISSING RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the relationship to the study medication is missing for an AE started after baseline, a causality of "Related" is assigned. Imputed values for relationship to study drug is used for incidence summary, while the actual values are presented in data listings.

13.6 MISSING DATE INPUTATION FOR ADVERSE EVENTS

- **Incomplete Start Date**

The following imputation rules apply to the case where the start date is incomplete (i.e., partially missing) for adverse events.

Missing day and month

If the year is same as the year of first day of study drug dosing, then the day and month of the start date of study medication will be assigned to the missing fields.

If the year is not the same as the year of first day of study drug dosing, then January 1 is assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure.

Missing day only

If the month and year are same as the year and month of first day of study drug dosing, then the start date of study drug dosing is assigned to the missing day.

If the month and year are not the same as the year and month of first day of study drug dosing, then the first day of the month is assigned to the missing day.

- **Incomplete Stop Date**

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If needed, the following imputation rules apply to the case where the end date is incomplete (i.e., partially missing) for adverse events. Other partial end date will not be imputed.

Missing day and month, or Missing month only

December 31 is assigned to the missing fields.

Missing day only

The last day of the month is assigned to the missing day.

Table 13.6-1 Imputation of the Analysis Adverse Event Start Date

Reported Date	Date of First Drug Intake	Analysis Date (Derived)
--/MM/YYYY	DD/MM/YYYY	
--/02/2008	14/02/2008	14/02/2008*
--/02/2008	14/02/2007	01/02/2008
--/02/2008	14/02/2009	01/02/2008
--/--/YYYY	DD/MM/YYYY	
--/--/2008	14/02/2008	14/02/2008
--/--/2008	14/02/2007	01/01/2008
--/--/2008	14/02/2009	01/01/2008
DD/--/---- --/MM/---- --/--/----		No imputation

Table 13.6-2 Imputation of the Analysis Adverse Event Stop Date

Reported Date	Analysis Date (Derived) *
--/MM/YYYY	31/MM/YYYY or 30/MM/YYYY or 29/MM/YYYY or 28/MM/YYYY
--/--/YYYY	31/12/YYYY
DD/--/----, or --/MM/----, or --/--/----	No imputation

*Death has to be taken into consideration when calculating this.

13.7 MISSING DATE IMPUTATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, including rescue medications, incomplete (i.e., partially missing) start date and/or stop date is imputed. When the start date and the stop date are both incomplete for a patient, impute the start date first.

- **Incomplete Start Date**

The following rules are applied to impute the missing start date. If the stop date is complete and the imputed start date is after the stop date, then the start date is imputed using the stop date.

Missing day and month

If the year of the incomplete start date is the same as the year of the first study drug dose date , then the day and month of the first dose is assigned to the missing fields.

If the year of the incomplete start date is not the same as the first dose date , then January 1 is assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure.

Missing day only

If the month and year of the incomplete start date are the same as the month and year of the first dose date, then the day of the first dose date is assigned to the missing day.

If the month and year of the incomplete start date are the same as the first dose date, then the first day of the month is assigned to the missing day.

- **Incomplete Stop Date**

The following rules are applied to impute the missing stop date, if needed. If the last dose date is missing, impute it with the last visit date. If the imputed stop date is before the start date (imputed or non-imputed start date), then the imputed stop date is replaced with the start date.

Missing day and month

If the year of the incomplete stop date is the same as the year of the last dose date, then the day and month of the last dose date is assigned to the missing fields.

If the year of the incomplete stop date is not the same as the year of the last dose date , then December 31 is assigned to the missing fields.

Missing month only

Treat day as missing and replace both month and day according to the above procedure.

Missing day only

If the month and year of the incomplete stop date are the same as the month and year of the last dose date, then the day of the last dose date is assigned to the missing day.

If the month and year of the incomplete stop date are not the same as the month and year of the last dose date, then the last day of the month is assigned to the missing day.

13.8 MISSING DATE IMPUTATION FOR LAST DOSE DATE

Imputed last dose date = earliest date of (last drug dispense date + number of days of drug dispensed, date of death, date of EOT/EOS visit, and other dates as appropriate).

13.9 CHARACTER VALUES OF CLINICAL LABORATORY PARAMETERS

If the reported value of a clinical laboratory parameter cannot be used in a statistical summary table due to, for example, that a character string is reported for a parameter of the numerical type, coded value needs to be appropriately determined and used in the statistical analyses. However, the actual values as reported in the database are presented in data listings.

Table 13.9 – 1. Example for Coding of Special Character Values for Clinical Laboratory Parameters

Lab Test	Possible Lab Results (in SI unit)	Coded Value for Analysis
Urinalysis: Glucose	= OR > 55, >= 55, > 0	Positive
	<= 0, Negative	Negative
Urinalysis: Ketones	= OR > 8.0, >=8.0, > 0	Positive
	<= 0, Negative	Negative
Urinalysis: pH	> 8.0, >= 8.0	8.0
	>= 8.5,	8.5
Urinalysis: Protein	= OR > 3.0, >=3.0, > 0	Positive
	<= 0	Negative