NCT #: NCT01890265

STATISTICAL ANALYSIS PLAN

STUDY TITLE:	**A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of FG-3019 in Patients with Idiopathic Pulmonary Fibrosis**
PROTOCOL NUMBER:	**Protocol FGCL-3019-067, Amendment 5.0**
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
Version	Part 2 (Treatment Extension) Final
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CONFIDENTIALITY STATEMENT

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Approvals

I have reviewed and accepted the information in this document to be a true and accurate representation of the Statistical Analysis Plan for analysis of extension data for Study FGCL-3019-067 (Part 2), Extended Treatment Period.

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Signature Significance

The following significance is lent to the signatures on the Approvals page of this document.

Signatory	**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

ADaM	Analysis Data Model
AE	Adverse event
CM	Concomitant medication
CTGF	Connective tissue growth factor
ECG	Electrocardiogram
EOS	End of study
EOT	End of treatment
EX	Extension
FG-3019	FibroGen-3019 (recombinant human monoclonal antibody)
FVC	Forced vital capacity
FVC (L)	FVC in litre
FVCpp	FVC % predicted
HAHA	Human anti-human antibody
HRCT	High resolution computed tomography
HRQoL	health-related quality of life
ICF	Informed consent form
IPF	Idiopathic pulmonary fibrosis
PEY	Patient exposure years
PK	Pharmacokinetic
PRO	Patient reported outcome
SAE	Serious adverse event
SAP	Statistical analysis plan
SGRQ	Saint Georges Respiratory Questionnaire
SDTM	Study Data Tabulation Model
TEAE	Treatment emergent adverse event

1 INTRODUCTION

The planned analyses for the Randomized Treatment Period are documented in Part 1 of the Statistical Analysis Plan (SAP) for study FGCL-3019-067: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of FG 3019 in Patients with Idiopathic Pulmonary Fibrosis. This is the part 2 of the SAP, which documents the planned analyses for the Extended Treatment Period. This document is based on the protocol Amendment 5.0 dated 12DEC2016.

In this document, only new definitions and rules will be described; the same defintions and rules described in the Part 1 of the SAP will not be repeated.

2 STUDY DESIGN (EXTENDED TREATMENT PERIOD)

2.1 Enrollment to Extended Treatment

Subjects Enrolled under the Original Protocol and Randomized to FG-3019

All subjects in Arm A whose FVC percent predicted value shows less than 3% absolute decrease from baseline in the Randomized Treatment Period will be offered participation in an Extended Treatment Period. These subjects may continue treatment until FVC percent predicted decreases 3% or more on two consecutive scheduled evaluations compared to the original pre-treatment baseline.

Subjects Enrolled Under Protocol Amendments and Randomized to FG-3019

All subjects in Arm A whose FVC percent predicted value is greater than the original pre-treatment baseline in the Randomized Treatment Period will be offered participation in an Extended Treatment Period and may continue treatment until FVC percent predicted is equal to or less than the pre-treatment baseline on two consecutive scheduled evaluations.

Subjects Randomized to Placebo

All subjects randomized to Placebo (Arm B) will be offered participation in the Extended Treatment Phase for 45 weeks. Placebo subjects in the extension study are treated identically to subjects randomized to FG-3019 in Amendment 1, except for the fact that the baseline for these patients is the time at which they are enrolled into the extension phase (Baseline for Placebo subjects is Week 48 value). Change in FVC percent predicted during the extended treatment phase will be compared to this new baseline. Those subjects whose FVC percent predicted value is either equal to or greater than the new baseline may continue treatment with FG-3019 until FVC percent predicted is equal to or less than the baseline on two consecutive scheduled evaluations.

Subjects in Substudy

Subjects in substudy are not eligible to enroll into the extended treatment.

2.2 Assessments in Extended Treatment Period

- FVC and FEV1 are assessed at 12-week intervals.
- HRCT scan of the chest is performed at 24-week interval during extension period.
- SGRQ questionnaire is administered at 12-week intervals.
- Electrocardiogram (ECG) is assessed at 24-week intervals.
- Laboratory samples for safety assessments are collected at 6-week intervals.
- Serum and plasma samples for biomarker tests (including CTGF) are collected at 24-week intervals.
- Plasma samples for assessing HAHA are collected prior to dosing on Day 1 of Extension Period and at the End of Study (EOS) safety follow-up.
- Adverse events, concomitant medications, procedures, non-drug therapies, oxygen use are collected from signing ICF through End of Study (EOS).

- Vital signs are measured at every clinical visit. On dosing days, vital signs are measured at pre-, intra-, and post-infusion.
- Physical examination is performed at 6-week intervals.

3 STUDY ENDPOINTS AND DEFINITIONS (EXTENDED TREATMENT PERIOD)

3.1 Study Endpoints

- Change from baseline in FVC (L) and FVC (% predicted) at each assessed time point
- Change from baseline in fibrosis score by quantitative HRCT at each assessed time point
- Change from baseline in HRQoL at each assessed time point.

3.2 Definitions of Endpoints in Extended Treatment Period

3.2.1 Efficacy Endpoints

For subjects who were originally randomized to FG-3019, efficacy endpoints are defined as change from the original baseline at study entry. These summaries will enable evaluation of long-term effect.

For subjects who were originally randomized to placebo and rolled over to active in extension, efficacy endpoints are defined as change from baseline as defined as the final assessment during the Randomized Treatment Period. These summaries will enable separate evaluation of effect of active treatment from placebo.

3.2.2 Study Drug Exposure and Treatment Compliance

Duration of year 1 exposure = date of last non-zero dose in year 1– date of first dose + 1.

Duration of extended treatment exposure = date last non-zero dose in extension – date of first dose in extension + 1.

Duration of entire study treatment exposure = date last non-zero dose in study – date of first dose in study + 1.

Number of infusions is defined as the number of non-zero dose infusions.

Compliance in each treatment year = (# of actual doses administered)/ (# of expected doses) * 100, where # of expected doses = (last dosing week)/3 + 1. All components in the formula are winthin each treatment year from Day 1 – EX year k to Weeks 45 or EOT in year k.

Overall compliance in entire study = (sum of # of actual doses administered in each treatment year)/ (sum of # of expected doses in each treatment year) * 100.

3.2.3 Adverse Events

In this SAP Part 2, treatment emergent AE (TEAE) will be defined for (a) the entire study, (b) the Randomized Treatment Period, and (c) the Extended Treatment Period.

TEAE in the Entire Study (TEAE)

TEAEs in the study are defined as <u>new</u> or <u>worsening</u> AEs that occurred in the window of first infusion and within 28 days of the last infusion of study drug, regardless of large gaps of treatment interruption.

TEAE in the Randomized Treatment Period (TEAE-R)

TEAEs during the randomized treatment period are defined as <u>new</u> or <u>worsening</u> AEs that occurred in the window of first dose of infusion of the blinded study drug (FG-3019 or placebo)

(Day 1) and within 28 days of the last infusion of FG-3019/placebo or before the first FG-3019 infusion in the extended treatment period, whichever occurs first.

TEAE in the Extended Treatment Period (TEAE-EX)

TEAEs-EX are defined as new or worsening AEs that occurred in the window of first infusion in Extension and within 28 days of the last infusion in Extension.

Below is an example of the three definitions of TEAE for multiple records of the same AE.

AE #	Period	Onset	AE	Severity	Serious -ness	Related to study drug?	TEAE	TEAE-R	TEAE-EX
1	Year 1	Screening	Headache	2	N	N	N	N	N
2	Year 1	Day 2	Headache	1	N	N	N	N	N
3	Year 1	Last Year 1 dose	Headache	2	N	Y	N	N	N
4	Year 1	10 days post last dose	Headache	3	Y	N	Y	Y	N
5	Year 1	45 days post last dose	Headache	4	Y	N	Y	Y	N
6	EX	Day 2-EX	Headache	2	N	Y	N	N	N
7	EX-2	Day 10 EX-2	Headache	1	N	N	N	N	N
Consoli-dated for Entire study summary			Headache	4	Y	Y	Y		
Consoli-dated for Year 1 summary			Headache	4	Y	Y		Y	
Consoli-dated for Extension summary			{none}	NA	NA	NA			N

3.2.4 Patient-Exposure-Years

Patient-Exposure-Years (PEY) is defined as the sum of all subjects' duration of follow-up in years, on FG-3019 or placebo respectively, for the entire study. A subject's duration of follow-up is defined as time from the first dose to the last follow-up recorded in the database. For those

who died, their date of death is the date of last follow-up. For subjects who are randomized to placebo and treated in extension, their last follow-up on placebo is defined as the date prior to Day 1-EX. For other subjects, date recorded on End-of-Study Disposition is the date of last follow-up.

3.2.5 TEAE and Mortality

TEAE and mortality will be reported in percentage per total number of subjects exposed.

4 GENERAL STATISTICAL CONSIDERATIONS

Efficacy and safety data will be summarized descriptive for subjects who entered extension and for all subjects who have been treated in the study. No formal statistical inference will be performed.

4.1 Analysis Populations

Extension Safety Population (Safety-EX) and Safety Population are the same defined as in the SAP Part 1.

4.2 Handling Dropouts and Missing Data

Missing values in the efficacy and safety parameters will not be imputed. All efficacy and safety will be summarized based on available observed data. Imputation will only be performed on missing or incomplete AE onset date or CM start/stop date. The same imputation algorithm described in SAP Part 1 will be used.

4.3 Definition of Baseline

For subjects who were randomized to FG-3019 arm, the original baseline defined in the Randomized Treatment Period as described in SAP Part 1 will be used. This definition will enable evaluation of long term treatment effect in safety and efficacy parameters.

For subjects who were randomized to placebo arm, baseline in Extension Period will be re-defined as last assessment prior to first dose in Extension on Day 1-EX. This will separate the effect of FG-3019 from placebo.

4.4 Efficacy Analysis Visit Window

The assessment intervals for the efficacy parameters (PFT, HRCT, and PRO) are the same in the Randomized Treatament Period and Extened Treatment Period, the same windowing rules described in SAP Part 1 will be used.

4.5 General Layout

For subjects who have been treated in extension, all safety and efficacy data, including both the Randomized Treatment Period and Extended Treatment Period, will be summarized descriptively by scheduled visit. All data will be presented in data listings.

5 STATISTICAL ANALYSES

5.1 Subject Disposition

The number of subjects in each study population will be summarized. The number of subjects who completed or discontinued the study as well as the reasons for early discontinuation will be summarized for subjects entered extension.

Subject who discontinued the study prematurely and the reasons will be listed.

5.2 Protocol Deviations

Protocol deviations occurred in the extension period will be summarized and presented in data listing for subjects treated in extension.

5.3 Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized and presented in data listing as described in Section 4.5.

5.4 Summary of Prior and Concomitant Medications

Concomitant medications and non-drug therapies administered during the study will be summarized by study period.

All medications and non-drug therapies will be presented in data listings for subjects treated in extension.

5.5 Summary of Study Drug Exposure and Treatment Compliance

Duration in days from first dose to last dose, number of doses, and dose amount in mg will be summarized and presented in data listing as described in Section 4.5.

5.6 Summary of the Efficacy Data in the Extension Period

Efficacy parameters, including change from baseline in FVCpp, FVC (L), HRCT fibrosis score, and SGRQ total and domain scores, are summarized descriptively at each scheduled visit for subjects who have been treated in extension.

5.7 Summary of Safety Data in the Extension Period and Overall Study

5.7.1 Summary of Treatment Emergent Adverse Events and Mortality

TEAE and mortality will be summarized for subjects who entered extension.

5.7.2 Summary of Other Safety Data

Other safety data including central laboratory data, vital signs, ECG, and physical examination will be summarized descriptively by visit for subjects who have received extended treatment.

6 CHANGES FROM THE PROTOCOL

- As documented in Note-To-File dated 05DEC2017 biomarker samples collected at Week 24 (pre-dose) and Week 48 at each extension year, are used to evaluate trough level of FG-3019 concentraction.

APPENDIX. GENERAL SPECIFICATIONS FOR SUBMISSION DATA

1. Study Data Tabulation Model (SDTM)

A new set of SDTM datasets, containing the entire study data, will be created. The set of SDTM datasets created for the Randomized Treatment Period is a subset of this set for the entire study.

Table A. Study Data Tabulation Model Datasets (SDTM)

SDTM Domain	SDTM Domain Description	SDTM Domain Structure	General Observation Class	Source Data Used	Key Variables
AE	Adverse Events	One record per adverse event per subject	Events	AE	STUDYID, USUBJID, AESTDTC, AEDECOD, AESPID
CM	Concomitant Medications	One record per recorded medication occurrence per subject	Interventions	CM, CMIPF	STUDYID, USUBJID, CMCAT, CMSPID, CMTRT, CMSTDTC
DD	Death Details	One record per subject	Findings	DTH	STUDYID, USUBJID, DDTESTCD
DM	Demographics	One record per subject	Special Purpose Domains	DM, EX, ICF, DTH, SITE_INV	STUDYID, USUBJID
DS	Disposition	One record per disposition status or protocol milestone per subject	Events	DS, ICF, DTH, EX	STUDYID, USUBJID, DSSTDTC, DSDECOD, DSSPID, EPOCH
DV	Protocol Deviations	One record per protocol deviations per subject	Events	DV	STUDYID, USUBJID, DVTERM
EC	Exposure as Collected	One record per protocol-specified study treatment per collected-dosing interval per subject	Interventions	EX	STUDYID, USUBJID, ECTRT, ECSTDTC, ECGRPID
EG	ECG Test Results	One record per ECG	Findings	EG	STUDYID,

		observation per visit per subject			USUBJID, EGTESTCD, VISITNUM
EX	Exposure	One record per constant dosing interval per subject	Interventions	EX	STUDYID, USUBJID, EXTRT, EXSTDTC
IE	Inclusion/Exclusion Criteria Not Met	One record per inclusion/exclusion criterion not met per subject	Findings	IE	STUDYID, USUBJID, IETESTCD
LB	Laboratory Test Results	One record per lab test per specimen per method per LOINC code per reason not done per visit per subject	Findings	eDT LB, RAND, LBC, LBPREG	STUDYID, USUBJID, LBCAT, LBTESTCD, VISITNUM, LBMETHOD, LBREASND, LBLOINC
MH	Medical History	One record per medical history event per time interval per subject	Events	MH	STUDYID, USUBJID, MHSPID, MHDECOD, MHSTDTC, MHENDTC
PC	Pharmacokinetic Concentrations	One record per time-point concentration or sample characteristic per analyte per subject	Findings	Source documents, PKC	STUDYID, USUBJID, PCTESTCD, VISITNUM, PCTPTNUM
PE	Physical Examination	One record per body system or abnormality per visit per subject	Findings	PE	STUDYID, USUBJID, PETESTCD, VISITNUM
PP	Pharmacokinetic Parameters	One record per PK parameter per time-concentration profile per modeling method per subject	Findings	Source documents	STUDYID, USUBJID, PPTESTCD, PPCAT, VISITNUM, PPTPTREF
PR	Procedures	One record per recorded procedure per occurrence per subject	Interventions	NDT, OU	STUDYID, USUBJID, PRCAT, PRTRT, PRSPID

QS	Questionnaires	One record per question per questionnaire per visit per subject	Findings	SGRQ, UCSD	STUDYID, USUBJID, QSTESTCD, VISITNUM
SC	Subject Characteristics	One record per characteristic per subject	Findings	DM	STUDYID, USUBJID, SCTESTCD
SE	Subject Elements	One record per actual Element per subject	Special Purpose Domains	SDTM.DM, SDTM.EX, SDTM.DS, SDTM.SV	STUDYID, USUBJID, TAETORD, SESTDTC
SU	Substance Use	One record per substance type per subject	Intervention	SUTOB	STUDYID, USUBJID, SUTRT
SV	Subject Visits	One record per actual visit per subject	Special Purpose Domains	All datasets including visits	STUDYID, USUBJID, VISITNUM
TA	Trial Arms	One record per planned Element per Arm	Trial Design	N/A	STUDYID, ARMCD, TAETORD
TE	Trial Elements	One record per planned Element	Trial Design	N/A	STUDYID, ETCD
TI	Trial Inclusion/Exclusion Criteria	One record per I/E criterion per protocol criteria version	Trial Design	N/A	STUDYID, TIVERS, IETESTCD
TS	Trial Summary	One record per Trial Summary parameter per occurrence	Trial Design	N/A	STUDYID, TSPARMCD, TSSEQ
TV	Trial Visits	One record per planned Visit per Arm	Trial Design	N/A	STUDYID, VISITNUM, ARMCD
VS	Vital Signs	One record per vital sign measurement per time point per visit per subject	Findings	VS, SC	STUDYID, USUBJID, VSTESTCD, VISITNUM, VSDTC
ZH	High Resolution Computed Tomography	One record per examination per location per time point per visit per subject	Findings	HRCT, TEXTCAD, TEXTVIS, IMQUAL	STUDYID, USUBJID, ZHCAT, ZHTESTCD, VISITNUM, ZHDTC,

					ZHLOC, ZHEVAL
ZI	IPF Confirmation	One record per IPF Confirmation per test per subject	Findings	IPFD	STUDYID, USUBJID, ZITESTCD
ZP	Pulmonary Function Tests	One record per test per time point per visit per result per subject	Findings	eDT PFT, RAND, ZP, MHPFT	STUDYID, USUBJID, ZPCAT, ZPTESTCD, VISITNUM, ZPDTC, ZPORRES

2 Analysis Data Model (ADaM)

A new set of ADaM datasets will be created to fit the required analyses for SAP Part 2.

Table B. Analysis Data Model (ADaM)

Dataset	Description	Structure	Keys
ADSL	Subject-Level Analysis Dataset	One record per subject	STUDYID, SUBJID
ADAE	Analysis Dataset Adverse Events	One record per subject per adverse event	STUDYID, SUBJID, AESTDTC, AEDECOD, AESPID
ADCM	Analysis Dataset Concomitant Medications	One record per subject per recorded medication occurrence	STUDYID, SUBJID, CMCAT, CMSPID, CMTRT, CMSTDTC
ADDD	Analysis Dataset Death	One record per subject per paramter	STUDYID SUBJID PARAMCD
ADEG	Analysis Dataset for ECG Test Results	One record per subject per visit	STUDYID, SUBJID, PARAMCD, AVISITN, ADT
ADEX	Analysis Dataset Exposure	One record per subject per parameter per visit	STUDYID, SUBJID, PARAMCD, AVISITN
ADHRCT	Analysis Dataset HRCT	One record per subject per measurement method per Lung Lobe per parameter per visit	STUDYID, SUBJID, PARAMCD, AVISITN, DTYPE ALOC
ADLB	Analysis Dataset Laboratory Test	One record per subject per category per	STUDYID, SUBJID, PARCAT1,

	Results	parameter per visit per normal range per result	PARCAT2, PARAMCD, AVISITN, ANRHI, AVAL
ADMH	Analysis Dataset Medical History	One record per subject per medical history per time interval of medical history	STUDYID, SUBJID, MHSPID, MHDECOD, MHSTDTC, MHENDTC
ADPC	Analysis Dataset PK Concentrations	One record per subject per visit per time point per parameter	STUDYID, SUBJID, AVISITN, ATPTN, PARAMCD
ADPE	Analysis Dataset Physical Examination	One record per subject per parameter per visit	STUDYID, SUBJID, AVISITN, PARAMCD
ADPF	Analysis Dataset Pulmonary Function Tests	One record per subject per parameter per time point per visit	USUBJID, SUBJID, PARAMCD, AVISITN, DTYPE, ADT, ATM
ADPP	Analysis Dataset Pharmacokinetic Parameters	One record per subject per parameter per visit	STUDYID, SUBJID, AVISITN, PARAMCD
ADPR	Analysis Dataset Procedures	One record per recorded procedure per occurrence per subject	STUDYID, SUBJID, PRTRT, PRSPID
ADQS	Analysis Dataset for Questionnaire	One record per subject per category per parameter per visit	STUDYID, SUBJID, PARCAT1, PARAMCD, AVISITN, VISITNUM
ADTTE	Analysis Dataset Time-to-Event	One record per subject per parameter	STUDYID, SUBJID, PARAMCD
ADVS	Analysis Dataset Vital Signs	One record per subject per parameter per time point per visit	STUDYID, SUBJID, PARAMCD, AVISITN, DTYPE, ADT, ATM, ATPTN