STATISTICAL ANALYSIS PLAN

STUDY TITLE:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy (Open-Label Extension)
PROTOCOL NUMBER:	FGCL-3019-079 OLE Amendment 8: 18 November 2020
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
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CONFIDENTIALITY STATEMENT

SIGNATURES AND APPROVALS

Approvals

I have reviewed and accepted the information in this document to be a true and accurate representation of the Statistical Analysis Plan.

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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.

CHANGE HISTORY

Version	Date	Description
1.0	5/2/2021	Original Final Version
1.1	5/7/2021	Minor edits
1.2	1/25/2023	Added section 11 for immunogenicity analysis
1.3	7/24/2023	Major changes: 1. Changed RCM to MMRM for all efficacy endpoints except for ppFVC 2. Removed ITT and added IGS analysis population 3. Changed Day 0 to Day 1 4. Updated analysis windows per protocol
2.0	10/12/2023	Final version v2.0

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List of Abbreviations

AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BIW	Twice weekly
BP	Blood Pressure
CBC	Complete blood count
CKD	Chronic kidney disease
CRF	Case report form
COVID-19	Coronavirus disease 2019
CRP	C-Reactive Protein
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EE	Efficacy Evaluable
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-Linked Immunosorbent Assay
EOT	End of Treatment
EOS	End of Study
EPO	Erythropoietin
HIV	Human immunodeficiency virus
HMP	Hepatic Monitoring Plan
HR	Heart Rate
IV	Intravenous
LLN	Lower Limit of Normal for a lab parameter
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximal expiratory pressure
MIF50	Maximal inspiratory flow at 50%

MIP	Maximal inspiratory pressure
mg	Milligram
MMRM	Mixed Model Repeated Measures
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NCS	Not clinically significant
NYHA	New York Heart Association
OLE	Open label extension
PEF	Peak expiratory flow
PFT	Pulmonary function test
PK	Pharmacokinetic
ppFVC	Percent predicted FVC
PRO	Patient reported outcome
PT	Preferred Term
PTT	Partial prothrombin time
ROM	Range of motion
RPM	Respirations per minute
RCM	Random coefficient model
SAE	Serious adverse event
SAP	Statistical analysis plan
SE	Standard error
SOC	System organ class
SDTM	Study Data Tabulation Model
TEAE	Treatment emergent adverse event
TLFs	Tables, listings and figures
ULN	Upper limit of normal
WHODrug	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Preface

This study is a single-arm, open-label extension (OLE) of Study FGCL-3019-079. The OLE period was designed to evaluate the long-term efficacy and safety of pamrevlumab in non-ambulatory DMD subjects who participated in the main phase of the study. Each subject in the OLE will receive pamrevlumab (35 mg/kg) intravenously (IV), every 2 weeks (Q2W) for up to 208 weeks. This dose was a continuation of the dose regimen evaluated during the main study period of FGCL-3019-079. At completion of the OLE subjects will be asked to return to the investigative site to complete final assessments with an End of Study (EoS) visit.

The parent study protocol FGCL-3019-079 provides detailed information on study drug formulation, storage, and administration.

This statistical analysis plan (SAP) summarizes statistical analyses of study data for the subjects who participated in the OLE period of Study FGCL-3019-079.

1.2. Purpose of the Analyses

The analyses will evaluate the long-term efficacy and safety of pamrevlumab in non-ambulatory DMD subjects who participated in the OLE period following completion of pamrevlumab treatment in the main period of FGCL-3019-079.

The OLE data will be summarized as part of the Study FGCL-3019-079 clinical study report.

2. STUDY DESIGN

This study is designed as the open-label extension (OLE) of the main study FGCL-3019-079. All subjects participating in the OLE must have completed treatment through the primary endpoint and completed the End of Treatment (EOT) visit of the main study FGCL-3019-079.

Each subject in the OLE receives pamrevlumab (35 mg/kg, every 2 weeks) for up to 208 weeks. The dosing period began on the first day of dosing with study treatment (Day 1) in the OLE, which is to be conducted simultaneously with, or within 7 days after the parent study EOT visit. The dosing period continued until Week 208/EOT.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective of this trial is to evaluate long-term efficacy and safety of pamrevlumab in non-ambulatory DMD subjects who have been previously treated with pamrevlumab for a minimum of 104 weeks.

4. STUDY ENDPOINTS

4.1. Efficacy Endpoints

The efficacy endpoints are:

Pulmonary assessment:

- Annual mean change in percent predicted forced vital capacity (ppFVC%) assessed by spirometry.

Performance assessments:

- Annual mean change from baseline in the total score of Performance of Upper Limb (PUL).
- Annual mean change from baseline in the grip strength of the hands extremities assessed by Hand Held Myometry (HHM)

Cardiac assessments:

- Annual mean change from baseline in cardiac fibrosis score assessed by Late Gadolinium Enhancement (LGE)
- Annual mean change from baseline in Left Ventricular Ejection Fraction percentage (LVEF %) assessed by MRI
- Annual mean change from baseline in Myocardial Circumferential Strain [Mean Peak Circumferential strain (MPCS) and Global Circumferential Strain (GCS) percentage] assessed by cardiac MRI

4.2. Safety Assessments

Treatment emergent adverse events (TEAEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related TEAEs serve as the safety assessments for this OLE.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Statistical Methodology

Continuous variables will be presented by descriptive statistics: n, mean, standard deviation, median, Q1-Q3, minimum, and maximum. Categorical variables will be tabulated by frequency count and percentage.

Lab results obtained from the central laboratory, rather than local laboratories, will be used for all efficacy and safety analyses. Some lab data are collected using local labs (in lieu of the ICON central lab) due to central lab kit shortages caused by the COVID-19 pandemic. In these cases, local lab values and reference ranges collected from CRFs will be integrated with central lab data when appropriate and feasible. Local lab values will be flagged in data sets and data listings to be differentiated from central lab values. Sensitivity analyses may be performed for key analyses of lab parameters without local lab values (e.g., set to missing).

Unless otherwise stated, all statistical tests will be two-sided hypothesis tests performed at the 5% level of significance for main effects and all confidence intervals will be two-sided 95% confidence intervals.

Unless otherwise specified, there will be no adjustments for multiple comparisons.

All data collected will be presented by data listings for review and substantiation of summary tables.

Safety and efficacy data will be summarized and presented by treatment group (pamrevlumab or source of external data, as applicable), and analysis visit in summary tables as appropriate.

All analyses will be performed using SAS® Version 9.4 or higher.

5.2. Analysis Populations

5.2.1. Safety Population (SAF-OLE)

The Safety population of OLE period (SAF-OLE) consists of all subjects who received at least one dose of study drug in the OLE period. The SAF population will be used in the analyses of all safety parameters.

All analyses for OLE period will be based on SAF-OLE if not specified otherwise.

5.2.2. Immunogenicity Analysis Set (IGS)

The Immunogenicity Analysis Set (IGS) contains all the Anti-Drug Antibody and/or Neutralizing Antibody (ADA/NAb) evaluable patients, who are in the SAF analysis set with at least one ADA/NAb sample (with reportable results) taken pre-treatment (i.e., a baseline sample) and at least one ADA/NAb sample (with reportable result) taken post-treatment in the OLE period.

5.3. Handling of Dropouts or Missing Data

All analyses will be based on observed data; missing data will not be imputed.

5.4. Additional Data Handling Rules and Presentation Specifications

5.4.1. Handling Missing/Incomplete AE Onset Date

If the AE onset date is incomplete or missing, the following rules will be applied to impute AE onset date.

- If year and month are present, only day is missing,

a. If AE onset Year/month = Day 1 Year/month, assign onset day = day part of Day 1 (Day 1 is the first infusion day);
b. If AE onset Year/month ≠ Day 1 Year/month, assign onset day = 1st of the month.

- If year is present, month and day are missing, or when only month is missing (treating day as missing),

a. If AE onset year = year of Day 1, assign onset date = month and day part of Day 1 date.
b. If AE onset year ≠ year of Day 1, assign onset date= January 1st.

- If onset date is completely missing, assign onset date = date of Day 1.

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.

5.4.2. Handling Missing/Incomplete Concomitant Medication Start/Stop Dates

For concomitant medications, including rescue medications, incomplete (i.e., partially missing) start date is imputed the same way as for the AE described above. When the start date and the stop date are both incomplete for a patient, impute the start date first.

Incomplete Stop Date

The following rules are applied to impute the missing stop date, if needed.

- If year is present, month and day are missing, or when only month is missing (treating day as missing)

a. If CM stop year = year of last dose, assign stop date = month and day part of of last dose date;
b. If CM stop year ≠ year of last dose, assign stop date= December 31st.

- If year and month are present, only day is missing,

a. If CM stop Year/month = Year/month of last dose date, assign stop day = day part of last dose date
b. If CM stop Year/month ≠ year of last dose, assign onset day = last day of the month.

- Impute CM end date even if 'ONGOING' is checked to report the CM treatment duration in the study if needed.

5.4.3. Definition of Baseline

- Baseline for the OLE period is the acceptable value from the last visit on or before the first dose date in OLE.

- Baseline for main study period is defined the same as in SAP for the main study period.

5.5. Analysis Visit Windows

Efficacy parameters will be summarized by analysis visit defined by the following assessment windows (Section 15). The date of the first dose will be considered as the date of Day 1 for all analysis. The analysis visit window for some safety assessments such as lab tests and vital signs are also defined in the same section.

5.6. Protocol Deviations

Protocol deviations of interest may include, but are not limited to, the following:

- Subjects who did not meet inclusion/exclusion criteria
- Subjects who received disallowed concomitant medications or non-drug therapy
- Subjects who missed important assessments or did not attend a visit as planned
- Subjects who did not receive adequate dosing.

The number and percentage of important protocol deviations will be categorized and tabulated as appropriate.

6. SUBJECT ACCOUNTABILITY AND DISPOSITION

The number and percentage of subjects who are dosed, completed the treatment or study, and prematurely discontinued will be summarized for the Safety Population.

Reasons for premature discontinuation as recorded on the Study Disposition page of the CRF will be summarized by number and percentage.

All subjects of the Safety Population, including subjects who discontinue prematurely from the study, will be listed with their treatment group, date and time of first and last dose, days in treatment, date of last visit, and reason for discontinuation.

A separate listing for the subjects who discontinue prematurely, date and time of first and last dose, days in treatment, date of last visit, and reason for discontinuation will be presented.

7. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

7.1. Demographics and Baseline Characteristics

Subject demographics, baseline characteristics, baseline disease characteristics, and baseline efficacy measures will be summarized. Baseline disease characteristics include general medical history, disease specific characteristics, and prior treatments. Baseline efficacy measures include PFT parameters, hand and arm functions, cardiac and muscle MRI parameters.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables. In addition, 25%-75% values of Biomarker will be presented. Frequency distributions (number and percentage of subjects) will be presented for categorical variables.

Descriptive statistics of baseline values for other parameters will be presented in their change from baseline tables.

Demographics and baseline characteristics of the study will be summarized using descriptive statistics.

Demographic variables will include age in years, sex (optional as all DMD subjects are male), race, and ethnicity. Age at baseline is defined as the age when signing inform consent:

$$\text{age} = \text{Year of Date of Informed Consent} - \text{Birth year}.$$

Other baseline characteristics include height, weight, side of dominant hand, BSA, and body mass index (BMI).

Computation formulas:

$$\text{BSA} = [\text{Weight}^{0.425}\ (\text{kg}) * \text{Height}^{0.725}\ (\text{cm})] \times 0.007184$$

$$\text{BMI} = \text{Weight (kg)} / (\text{Height (m)})^2$$

7.2. Medical History

Medical history, including allergies and surgeries, will be tabulated in system organ class (SOC) and preferred term (PT) using MedDRA version 26.0 or higher.

8. TREATMENTS AND MEDICATIONS

8.1. Study Drug Exposure

The number and percentage of subjects who receive study medication will be summarized.

Duration in weeks from first infusion to last infusion, calculated as (last dose date – first dose date+1)/7, will be summarized by the categories as follows:

<= 26 weeks

>26 weeks to <=52 weeks

>52 weeks to <=78 weeks

>78 weeks to <=104 weeks

>104 weeks to <=156 weeks

>156 weeks to <=208 weeks

>208 weeks

The number of infusions and average infusion dose amount in mg and mg/kg, any interruption during infusion (Y/N), and reason for missed dose or interruption will be summarized.

The compliance will be presented as % of actual doses of infusion administered out of the expected total dose of infusions during study. Compliance = (actual doses received / expected doses during study) * 100%. Treatment compliance will be summarized as a continuous variable and as a categorical variable (<70%, 70% -<80%, 80% - 90%, and >90%).

Duration of exposure, weekly exposure and total study drug exposure will be tabulated.

8.2. Concomitant Medications

The historical use of the medications is summarized using descriptive statistics for the Safety population.

Medications recorded on the Concomitant Medication CRF are classified in the analysis dataset in the following categories:

- Concomitant medications - medications that are used concomitantly with the study drug, which are defined as medications that were not stopped before the first infusion.
- Use of corticosteroids

Concomitant medications are summarized by ATC class and preferred term . Subjects reporting more than one use of the same medication will be counted only once in the summary tables.

All medications captured in Concomitant Medication CRF, as well as Non-Drug Therapies CRF are presented in data listings.

9. EFFICACY ANALYSIS

9.1. Efficacy Endpoints

The Efficacy Endpoints are:

Pulmonary assessment:

- Annual mean change in percent predicted forced vital capacity (ppFVC%) assessed by spirometry.

Performance assessments:

- Annual mean change from baseline in the total score of Performance of Upper Limb (PUL).
- Annual mean change from baseline the Grip strength of the hands extremities assessed by Hand Held Myometry (HHM).

Cardiac assessments:

- Annual mean change from baseline in cardiac fibrosis score assessed by Late Gadolinium Enhancement (LGE).
- Annual mean change from baseline in Left Ventricular Ejection Fraction percentage (LVEF %) assessed by MRI.
- Annual mean change from baseline in Myocardial Circumferential Strain [Mean Peak Circumferential strain (MPCS) and Global Circumferential Strain (GCS) percentage] assessed by cardiac MRI.

In addition to the analysis of annual mean changes of the above efficacy endpoints with random coefficient model (RCM), the change from baseline in the following efficacy endpoints of PUL, grip strength, LVEF%, and cardiac MRIs including cardiac fibrosis score assessed by Late Gadolinium Enhancement (LGE), and Myocardial Circumferential Strain [Global Circumferential Strain (GCS)], will be analyzed with Mixed Model for Repeated Measures (MMRM) at Week 48/52, Week 96/104, Week 144/156, and Week 192/208 per the schedule, without assuming linear trajectories by disease progression.

9.2. Analysis Methods for Efficacy Endpoints

Unless otherwise noted, long-term treatment effects of all efficacy endpoints at each timepoint will be summarized and analyzed from the baseline of the main study through the last visit in the extension phase. Change from baseline values in efficacy endpoints will be analyzed with MMRM Annual rate of change from baseline using Random Coefficient Model (RCM) analysis, and the estimated change from baseline values at year 1 through year 4 described in the following sub-sections will be presented.

The sponsor will conduct an exploratory comparison of disease progression of FGCL-3019-079 clinical trial participants with natural history data of patients with non-ambulatory DMD. If

warranted, analyses adjusting for matching on established baseline prognostic factors will be conducted under a separate SAP.

9.2.1. Descriptive Summary

Continuous variables will be presented by descriptive statistics: n, mean, standard deviation (SD), standard error (SE), median, 25th and 75th percentile, minimum, and maximum. The 2- sided 95% confidence interval for the mean and median will be presented as appropriate.

Categorical variables will be tabulated by frequency count and percentage. The confidence interval for the proportions for each will be calculated using the Clopper-Pearson method as appropriate.

9.2.2. Annual Change from Baseline to Week 208 in Efficacy Endpoints with RCM

The following endpoints will be analyzed with the same RCM analysis method.

1. Annual mean change from baseline in the Percent Predicted FVC (ppFVC)
2. Annual mean change from baseline in the total score of Performance of Upper Limb (PUL)
3. Annual mean change from baseline the Grip strength of the hands extremities assessed by Hand Held Myometry (HHM)
4. Annual mean change from baseline in cardiac fibrosis score assessed by Late Gadolinium Enhancement (LGE)
5. Annual mean change from baseline in Left Ventricular Ejection Fraction percentage (LVEF %) assessed by MRI
6. Annual mean change from baseline in Myocardial Circumferential Strain [Mean Peak Circumferential strain (MPCS) and Global Circumferential Strain (GCS) percentage] assessed by cardiac MRI

9.2.2.1. Analysis Method

Annual mean change from baseline in the above efficacy endpoints each will be analyzed using Random Coefficient Model (RCM) analysis, and the estimated annual change from baseline values at year 1 through year 4 in the OLE period will be presented.

The model will include continuous variable avisityr (calculated as the elapsed days of assessment date from baseline date in the unit of year) and baseline endpoint as fixed effects, while the intercept and avisityr are included as random effects.

The unstructured covariance structure for the within-patient errors in the model will be applied first. The by-treatment-group option is included to the covariance pattern to improve the model efficiency.

If the algorithm for unstructured covariance pattern does not converge, the following covariance structures will be tested in sequence until the model converges: heterogeneous Toeplitz, homogeneous Toeplitz, first-order autoregressive, compound symmetry, and variance component. The sandwich estimator will be used if there is convergence issue. If the model does not converge for all covariance structures listed above, some least significant factors or interaction terms ($p>0.05$)

can be excluded from the model to achieve convergence. The revised model with fewer factors or interaction terms will be tested using the same sequence as specified above.

When the random effects model does not converge or do not have a positive definite Hessian, the fixed effects instead of random effects for the intercept and slope will be performed instead.

The LSMean (SE) and 95% CI for annual change (slope) as well as estimated changes from baseline at year-1, year 2, year 3 and year 4 (regarding week 52, week 104, week 156 and week 208) will be presented.

9.2.2.2. Handling of Intercurrent Events:

Treatment discontinuation (such as: due to AEs, Lost to Follow-Up, Withdrawal by subject, Physician Decision, Protocol Deviations, etc.): treatment policy: the occurrence of the intercurrent event is irrelevant. All observed values will be used regardless of whether or not the inter-current event occurs.

9.2.3. Change from Baseline in Efficacy Endpoints with MMRM

The following efficacy endpoints will be analyzed with MMRM method.

1. At Week 48, Week 96, Week 144, and Week 192
    a. Change from baseline in PUL total score, including middle and distal score
    b. Change from baseline in grip strength. The grip strength should be reported by dominant and non-dominant hand separately.
2. At Week 52, Week 104, Week 156, and Week 208
    a. Change from baseline in LVEF%
    b. Change from baseline in cardiac MRIs including cardiac fibrosis score assessed by Late Gadolinium Enhancement (LGE)
    c. Change from baseline in Myocardial Circumferential Strain [Global Circumferential Strain (GCS)]

9.2.3.1. Analysis Method

The observed and change from baseline in the above efficacy endpoints each will be summarized by analysis visit and analyzed using MMRM with visit, baseline, and age with appropriate covariance matrix for the within subject covariance over time.

If the algorithm for unstructured covariance pattern does not converge, the following covariance structures will be tested in sequence until the model converges: heterogeneous Toeplitz, homogeneous Toeplitz, first-order autoregressive, compound symmetry, and variance component. The sandwich estimator will be used if there is convergence issue. If the model does not converge for all covariance structures listed above, some least significant factors or interaction terms ($p>0.05$) can be excluded from the model to achieve convergence. The revised model with fewer factors or interaction terms will be tested using the same sequence as specified above.

9.2.3.2. Handling of Intercurrent Events:

Treatment discontinuation (such as: due to AEs, Lost to Follow-Up, Withdrawal by subject, Physician Decision, Protocol Deviations, etc.): treatment policy: the occurrence of the intercurrent event is irrelevant. All observed values will be used regardless of whether the inter-current event occurs.

9.2.4. Exploratory Analysis - Comparison with the CINRG natural history data

Efficacy endpoints: % predicted FCV (ppFVC), LVEF, and grip strength in dominant hand will be compared with a subset of CINRG DMD Natural History study (DNHS) data with all 36 subjects using a random coefficient model (RCM). The other outcome measures including Performance of Upper Limb (PUL), cardiac fibrosis by LGE, and Myocardial Circumferential Strain [Mean Peak Circumferential strain (MPCS) and Global Circumferential Strain (GCS) percentage] assessed by cardiac MRI are not available in CINRG data and therefore will not be compared.. The RCM model will use efficacy data from both the main and OLE periods and include continuous variable avisityr (calculated as the elapsed days of assessment date from main study baseline date in the unit of year), treatment trt (079 subjects as treated with trt = 1, and subjects in CINRG data as control with trt =0), the interaction term of trt and avisityr, and baseline endpoint as fixed effects, while the intercept and avisityr are included as random effects. The strategy for covariance structure for the within-patient errors in the model is the same as what is described in Section 9.2.2.1. The LSMean (SE) for annual change (slope) as well as LSMean (SE) and 95% CI of treatment differences between pamrevlumab and control of estimated changes from baseline at year 1, year 2, year 3 and year 4 in the OLE period will be presented. The sample SAS code is provided in Appendix 2.

Line plots of each subject's efficacy trajectory compared with the mean plot of the CINRG will be provided.

10. SAFETY ANALYSIS

10.1. Adverse Events

All reported AEs will be presented in listings. For the OLE period of the 3019-079 study, the treatment emergent period of safety reporting for the Clinical Study Report (CSR) is defined as from the first infusion date to the last infusion date + min (60 days, EOS date -last infusion date+1) for those subjects in the open label extension (OLE) period.

Number (%) of subjects with a treatment emergent adverse events (TEAEs) in the treatment emergent period of safety reporting (OLE period) will be summarized by system organ class (SOC) and preferred term (PT). The summary tables will be sorted alphabetically by SOC and by decreasing order of frequency of PT within each SOC. A subject with multiple adverse events within a SOC is only counted once in this SOC. Similarly, a subject with multiple adverse events within a PT is only counted once in this PT.

The exposure adjusted incidence rate, number of subjects with the event/total patient exposure years (PEY)*100, will be summarized, system organ class (SOC) and preferred term (PT).

The patient exposure years (PEY), (last infusion date – first infusion date + 1)/365.25, for each subject will be summed to calculate the total patient exposure years. The summary tables will be sorted alphabetically by SOC and by decreasing order of frequency of PT within each SOC. A subject with multiple adverse events within a SOC is only counted once in this SOC. Similarly, a subject with multiple adverse events within a PT is only counted once in this PT. In addition to listing of all reported AEs and summary of all TEAEs, the following TEAE summaries will be provided:

- TEAEs
- TEAEs (grade 3 and higher per CTCAE)
- TEAE leading to treatment discontinuation
- TEAE and relationship to FG-3019 (pamrevlumab)
- TEAE and severity
- TESAE and relationship to FG-3019 (pamrevlumab)
- Most frequent (non-serious) TEAEs (>=5%)
- Listing of Deaths
- Listing of Serious Adverse Events
- Listing of TEAE leading to treatment discontinuation

In addition, special safety events such as hypersensitivity, anaphylactic and infusion reactions will be included.

10.2. Clinical Laboratory Assessments

Blood samples are drawn for the following analyses: complete blood count, gamma glutamyl transferase (GGT), total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), and albumin, creatine kinase (CK), and cystatin C.

Laboratory test results and change from baseline are summarized by analysis visit.

CTCAE grade 3 or higher lab test results will be considered potentially clinically significant. These results are summarized and presented in a data listing.

Shift tables to summarize changes from baseline to each visit in CTCAE categories are tabulated. Shift from baseline to most severe CTCAE category during the study is also summarized.

The Baseline for the laboratory parameters will be taking from EOS Laboratory value of the Parent study 079.

Laboratory values out of normal range, in particular, panic laboratory parameter / values will be listed.

10.3. Vital Signs

Pulse (beat/min), diastolic and systolic blood pressure (mmHg), respiration (breaths/min), and temperature (C) will be summarized for selected analysis visit.

10.4. Physical Examination

Physical examination results (complete and targeted) will be listed by subject, visit, and body system.

10.5. Electrocardiogram

Number (%) of subjects with ECG results (normal/abnormal/Clinically Significant) will be summarized by analysis visit.

10.6. Special Safety Events

Treatment-emergent special safety events including:

1. Hypersensitivity (any time)
2. Infusion reactions (on day of infusion or 1 day post any study drug infusion)
3. Anaphylactic reactions (on day of infusion or 1 day post any study drug infusion)

Items 1 and 2 include both hypersensitivity and angioedema events. Both items will be listed and summarized similarly to TEAEs.

Items 3 uses a modified SMQ to retrieve events under anaphylactic reactions and will be listed and summarized by treatment and PT only.

The preferred term list for these special safety events will be finalized prior to database lock.

11. INTERIM ANALYSIS

Not applicable.

12. IMMUNOGENICITY ANALYSIS

Analysis of immunogenicity data will be based on IGS. Analysis dataset and data listing will include all available Human Anti-Human Antibody (HAHA, ADA) samples. The following terms and definitions are implemented.

12.1. Terms and Definitions

12.1.1. Sample ADA Status:

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment.
- Baseline ADA-negative sample: ADA is not detected in the last sample before initiation of treatment.
- **Treatment-emergent ADA-Positive**: Meets definition of treatment-induced or treatment-boosted ADA. After initiation of treatment,
  - **Treatment-induced ADA-Positive**: a post-treatment positive ADA is detected in a subject for whom pre-treatment ADA assessment is either negative or not assessable, or
  - **Treatment-boosted ADA-Positive**: pre-existing ADA were boosted to a higher level following study treatment, i.e. pre-treatment positive ADA titer was boosted by at least 2 dilution steps (4-fold) following study treatment.
- ADA-negative sample: After initiation of treatment, ADA is not ADA-positive sample relative to baseline.

Next, using the sample ADA status, subject ADA status is defined.

12.1.2. Subject ADA Status:

- Baseline ADA-positive subject: A subject with baseline ADA-positive sample.
- ADA-positive subject: An evaluable subject with at least one treatment-emergent ADA sample at any time during the study.
- Neutralizing-positive: At least one treatment-emergent ADA-positive sample with neutralizing antibodies detected (if available).
- ADA-negative subject: An evaluable patient without a treatment-emergent ADA-positive sample during the study.

12.2. Statistical Analysis for Characterization of ADA Immune Response

12.2.1. Incidence of ADA

- Percentage of treatment-emergent ADA patients for the defined study period, where the denominator is the number of ADA evaluable patients in the respective treatment arm and/or subgroup.
- Number (%) of subjects will be reported for the following parameters based on evaluable subjects:
- Baseline ADA-positive
- ADA-positive (Treatment-induced, Treatment-boosted)
- Neutralizing Positive (if available)
- ADA-negative
- ADA prevalence: Percentage of treatment-emergent ADA patients at any given timepoint, where the denominator is the number of ADA evaluable patients in the respective treatment arm and/or subgroup at that timepoint.
- A listing of all ADA assessments will be provided.
- Additionally, a separate listing of ADA assessments for all neutralizing antibody (NAb)-positive subjects will be provided (if available).

12.2.2. ADA Titer Kinetics

All ADA-positive subjects will be included in the analysis.

- Summary statistics of subject-level ADA titers using the maximum titer value within an ADA positive subject will be presented for baseline ADA-negative subjects and baseline ADA positive subjects. The median, interquartile range, and range of the maximum titers will be reported. For ADA-positive subjects with baseline ADA-positive sample, the median and interquartile range of the fold increase from baseline in titer (ratio of maximum post-baseline titer to baseline titer) will also be reported. Graphical presentation of the summary data may be provided using boxplots, as appropriate.
- For sample-level ADA titers, boxplots of ADA titers at each assessment timepoint will be provided, as appropriate, to demonstrate whether the ADA levels tend to change over time during the treatment, along with ADA incidence at each assessment timepoint.
- Spider plots may be considered to show the trend of ADA titer over time for subjects with >/= 5 ADA results by splitting subjects into multiple spider plots (eg, ≈ ≤10 per plot, approximately.

13. CHANGES FROM PROTOCOL

- The date of the first dose in the OLE period will be considered as the date of Day 1 for all analyses during the OLE period, instead of Day 0.
- Efficacy parameters, including change from baseline of the main study in ppFVC, PUL, grip strength, LVEF%, and cardiac MRIs including cardiac fibrosis score assessed by Late Gadolinium Enhancement (LGE), and Myocardial Circumferential Strain [Global Circumferential Strain (GCS)], will be analyzed at Week 48/52, Week 96/104, etc. in the OLE period using Mixed Model for Repeated Measures (MMRM) additionally.

14. REFERENCES

1. Mayhew A, Mazzone ES, Eagle M, et al. Development of the Performance of the Upper Limb module for Duchenne muscular dystrophy. Dev Med Child Neurol 2013;55:1038–45.
2. Pane M, Mazzone ES, Fanelli L, et al. Reliability of the Performance of Upper Limb assessment in Duchenne muscular dystrophy. Neuromusc Disord 2014;24:201-206.
3. Hankinson JL, Odencrantz JR, Fedan KB, Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999; 159:179 – 187.
4. Mayer OH, Finkel RS, Rummey C et al. Characterization of Pulmonary Function in Duchenne Muscular Dystrophy. Pediatr Pulmonol. 2015; 50:487–494

15. APPENDICES

APPENDIX 1. ANALYSIS VISIT WINDOWS

Table 1: Assessment Windows for PFT

Analysis Visit	Window
Baseline	Value at the visit on or prior to the first dose of study drug Target day=1, window = $[L_0, H_0] = [--,1]$
Week X	X = 24*K, k=1, 2, …, 7 Target day = 7 * X + 1 Window = $[L_K, H_K] = [H_{K-1}+1$, Target Day+24*7/2-1]
Week 192	$[L_8 = H_7+1 = 1261$, **]

**** There will be no upper bound; all assessments will be included.**

Table 2: Assessment Windows for Muscle Function Tests

Analysis Visit	Window
Baseline	Value at the visit on or prior to the first dose of study drug Target day=1, window = $[L_0, H_0] = [--,1]$
Week X	X = 12*K, k=1, 2, …, 16 Target day = 7 * X + 1 Window = $[L_K, H_K] = [H_{K-1}+1$, Target Day+12*7/2-1]
Week 204	$[L_{17} = H_{16} +1=1387$, **]

**** There will be no upper bound; all assessments will be included.**

Table 3: Assessment Windows for Cardiac MRI

Analysis Visit	Window
Baseline	Value at the visit on or prior to the first dose of study drug Target day=1, window = $[L_0, H_0]$ = [--,1]
Week X	X = 52*K, k=1, 2, 3 Target day = 7 * X + 1 Window = $[L_K, H_K]$ = $[H_{K-1}+1$, Target Day+52*7/2-1]
Week 208	$[L_4 = H_3 +1$= 1275, **]

*** There will be no upper bound; all assessments will be included.**

Table 4: Assessment Windows for Vital Signs

Analysis Visit	Window
Baseline	Baseline are defined as the average of last Screening and Week 0 pre-infusion measurements. Target day=1, window = $[L_0, H_0]$ = [--,1]
Week X	X = 2*K, k=1, 2, 3, …, 105 Target day = 7 * X + 1 Window = $[L_K, H_K]$ = $[H_{K-1}+1$, Target Day+6]

***The last visit window will not have an upper bound; all assessment will be included.**

Table 5: Assessment Windows for Labs Tests

Analysis Visit	Window
Baseline	Value at the visit on or prior to the first dose of study drug Target day=1, window = $[L_0, H_0]$ = [--,1]
Week X	X = 24*K, k=1, 2, …, 8 Target day = 7 * X + 1 Window = $[L_K, H_K]$ = $[H_{K-1}+1$, Target Day+24*7/2-1]
Week 210	$[L_9 = H_8 +1$= 1408, **]

*** There will be no upper bound; all assessments will be included.**

All scheduled and unscheduled assessments are included in the by-visit summary. If more than two assessments are available in the same window, the last assessment will be used in the by- visit summary.

If any visit is missed, assessments should be performed as soon after the missed visit as feasible. Missed infusions will not be replaced.

Pamrevlumab infusion is NOT to be administered at week 208 (EOT).

APPENDIX 2. SAMPLE SAS CODE FOR RCM ANALYSIS

SAS code for this model, using the primary endpoint ppFVC as example, is provided below.

```
/*Random Coefficient Model (RCM) to estimate the change at year 1, 2, 3 and
4*/

/*avisityr is the actual number of years from Day 1, avisityr=4 will be
the change from baseline at year 4 */

/* fvc0= baseline ppFVC, should be used for change in FVC */

/* &meanfvc0= the mean of the baseline ppFvc           */


proc mixed data = fvc_obs;
  class subjid;
  model chgfvc = avisityr fvc0/solution cl covb outp=pred_fvc cl;
  random intercept avisityr /subject=subjid type=CS;
  ESTIMATE 'Change from Baseline at Year 1' intercept 1 avisityr 1 fvc0
  &meanfvc0 / CL;
  ESTIMATE 'Change from Baseline at Year 2' intercept 1 avisityr 2 fvc0
  &meanfvc0 / CL;
  ESTIMATE 'Change from Baseline at Year 3' intercept 1 avisityr 3 fvc0
  &meanfvc0 / CL;
  ESTIMATE 'Change from Baseline at Year 4' intercept 1 avisityr 4 fvc0
  &meanfvc0 / CL;
  ods output SolutionF=mxparms CovB=mxcovb Estimates=chgfrbl;
run;
```

Sample SAS code for comparison 079 OLE data (trt = 1) with CINRG (trt = 0).

```
PROC MIXED DATA = final;
        CLASS trt SUBJID ;
        MODEL chg = trt|avisityr base/ SOLUTION DDFM=KR;
        RANDOM intercept avisityr / SUBJECT =SUBJID TYPE=UN GROUP= trt;

        LSMEANS trt/ at avisityr = 1 PDIFF CL;
        LSMEANS trt/ at avisityr = 2 PDIFF CL;
        LSMEANS trt/ at avisityr = 3 PDIFF CL;
        LSMEANS trt/ at avisityr = 4 PDIFF CL;

        ods output LSMeans=LSMeans_chg diffs=diffs_chg;
RUN;
```

Statistical Analysis Plan
Addendum

TITLE PAGE

PROTOCOL TITLE:	A Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy (DMD)
PROTOCOL NUMBER:	Protocol FGCL-3019-079
STUDY SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
STUDY DRUG:	Pamrevlumab
INDICATION:	Duchenne Muscular Dystrophy (DMD)
SAP VERSION	Addendum v1.1
RELEASE DATE	August 08, 2023

SIGNATURES AND APPROVALS

Approvals

I have reviewed and accepted the information in this document to be a true and accurate representation of the Statistical Analysis Plan.

*Signature: see appended final page for 21CFR Part 11 compliant approval

Initiator:

Signature [redacted] Date

Reviewer:

Signature [redacted] Date

Signature [redacted] Date

Signature [redacted] Date

Signature [redacted] Date

Signature [redacted] Date

Signature [redacted] Date

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(s) are 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.

1. INTRODUCTION

Study FGCL-3019-079 has reached DBL and an interim CSR has been completed. There was an error in p-value reporting in the original SAP which requires an amendment to all related tables and figures. The update is provided in this SAP addendum.

Furthermore, as ADA samples were analyzed after the interim CSR, the analysis and reporting of ADA will be included in this SAP.

2. UPDATE TO THE ORIGINAL SAP

Reason for change:

The original approved SAP (version 1.0, dated June 25, 2020) specified 2-sided p-values to be reported for confidence intervals. However, the SAS function PROBT specified in SAP version 1.0 Appendix 1 and errata to the SAP returned a 1-sided p-value. The following amendments are made to correct related p-values.

In SAP Appendix I (on page 24, box on the left side below): the δ (or delta) should be (m1-m2) and t-test statistics should be (m1-m2)/se.

Two Sample Test statistics $\delta = \frac{(m_1 - m_2)}{se}$

T-test:

95% CI: $\delta \pm t(\delta, df) * se$

$p = t(\delta, df)$ (SAS function: $probt(\delta, df)$.

Please note that if $\delta \leq 0$, p-value=p; if δ>0, p-value=1-p.

ERRATA TO THE SAP

Two Sample Test statistics, delta= (m1-m2)

T-test: t=(m1-m2)/se

95% CI: delta +/- tinv(0.975, df)*se

(SAS function: p= probt(t, df) to get the p-value for the t-test.

Please note that if delta <= 0, p-value=p; if delta>0, p-value=1-p.

In Errata to SAP (on Page 38, right side box above), which was not signed off with any signatories, δ (or delta) and t-test statistics were corrected, however, the p-value was still 1-sided.

To correct this 1-sided p-value issue, the following highlighted in yellow is the only update to the Errata to SAP, where the p-value is multiplied by 2 and clarified as "2-sided".

(SAS function: p= 2*probt(t, df) to get the 2-sided p-value for the t-test.

Please note that if delta <= 0, p-value=p; if delta>0, p-value=1-p).

In addition, in section 4.6.6.2 of the original SAP, the sentence "the results for the PUL total score will be compared with the results from Ricotti, 2019" shall be removed, since different versions of PUL were used.

Since all secondary endpoints are "Change from Baseline to Week 104", the estimate of annual change for some secondary endpoints will not be reported due to data and/or analysis model limitations.

3. IMMUNOGENICITY ANALYSIS

3.1. Immunogenicity Analysis Set (IGS)

The Immunogenicity Analysis Set (IGS) contains all the ADA/NAb evaluable patients, who are in the SAF analysis set with at least one ADA/NAb sample (with reportable results) taken pre-treatment (i.e., a baseline sample) and at least one ADA/NAb sample (with reportable result) taken post-treatment.

Analysis of immunogenicity data will be based on IGS. Analysis dataset and data listing will include all available Human Anti-Human Antibody (HAHA, ADA) samples. The following terms and definitions are implemented.

3.2. Terms and Definitions

3.2.1. Sample ADA Status:

- Baseline ADA-positive sample: ADA is detected in the last sample before initiation of treatment.
- Baseline ADA-negative sample: ADA is not detected in the last sample before initiation of treatment.
- **Treatment-emergent ADA-Positive**: Meets the definition of treatment-induced or treatment-boosted ADA. After initiation of treatment,
  - **Treatment-induced ADA-Positive**: a post-treatment positive ADA is detected in a subject for whom pre-treatment ADA assessment is either negative or not assessable, or
  - **Treatment-boosted ADA-Positive**: pre-existing ADA was boosted to a higher-level following study treatment, i.e. pre-treatment positive ADA titer was boosted by at least 2 dilution steps (4-fold) following study treatment.
- ADA-negative sample: After initiation of treatment, ADA is not treatment-emergent ADA-positive.

Next, using the sample ADA status, subject ADA status is defined.

3.2.2. Subject ADA Status:

- Baseline ADA-positive subject: A subject with baseline ADA-positive sample.
- ADA-positive subject: An evaluable subject with at least one treatment-emergent ADA sample at any time during the study.
- Neutralizing-positive: At least one treatment-emergent ADA-positive sample with neutralizing antibodies detected (if available).
- ADA-negative subject: An evaluable patient without a treatment-emergent ADA sample during the study.

3.3. Statistical Analysis for Characterization of ADA Immune Response

3.3.1. Incidence of ADA

- Percentage of treatment-emergent ADA patients for the defined study period, where the denominator is the number of ADA evaluable patients in the respective treatment arm and/or subgroup.
- Number (%) of subjects will be reported for the following parameters based on evaluable subjects:
  - Baseline ADA-positive
  - ADA-positive (Treatment-induced, Treatment-boosted)
  - Neutralizing Positive (if available)
  - ADA-negative
- **ADA prevalence**: Percentage of treatment-emergent ADA patients at any given timepoint, where the denominator is the number of ADA evaluable patients in the respective treatment arm and/or subgroup at that timepoint.
- A listing of all ADA assessments will be provided.
- Additionally, a separate listing of ADA assessments for all neutralizing antibody (NAb)-positive subjects will be provided (if available).

3.3.2. ADA Titer Kinetics

All ADA-positive subjects will be included in the analysis.

- Summary statistics of subject-level ADA titers using the maximum titer value within an ADA positive subject will be presented for baseline ADA-negative subjects and baseline ADA positive subjects. The median, interquartile range, and range of the maximum titers will be reported. For ADA-positive subjects with baseline ADA-positive samples, the median and interquartile range of the fold increase from baseline in titer (ratio of maximum post-baseline titer to baseline titer) will also be reported. Graphical presentation of the summary data may be provided using boxplots, as appropriate.
- For sample-level ADA titers, boxplots of ADA titers at each assessment timepoint will be provided, as appropriate, to demonstrate whether the ADA levels tend to change over time during the treatment, along with ADA incidence at each assessment timepoint.
- Spider plots may be considered to show the trend of ADA titer over time for subjects with >/= 5 ADA results by splitting subjects into multiple spider plots (e.g., $\approx \leqslant 10$ per plot, approximately.

3.4. Clinical Implication of ADA Immune Response

3.4.1. Safety

- Effect of ADA response on safety will be explored by examining the frequency and type of AEs of interest, including (1) Total TEAEs, (2) Drug Hypersensitivity, and (3) Infusion Reactions. For each category of AEs, summary tables for incidence will be provided for each of the preferred terms and overall within a category by ADA status, if the number of ADA-positive subjects is of sufficient size (e.g., at least ≈10 subjects). Otherwise, individual subject's safety profile will be examined and described based on a listing.
- Listings of AEs will be provided. These listings will also indicate the study day and study period of the positive responses.

3.4.2. Efficacy

- The primary efficacy endpoint will be presented by ADA status.
- Efficacy listings for all positive subjects (relative to baseline) will be provided. These listings will also indicate the study day and study period of the positive responses.