1. PROTOCOL AND AMENDMENTS

Original Study Protocol (16 June 2015)

Study Protocol Amendment 1.0 (31 August 2015)

Study Protocol Amendment 2.0 (06 May 2016)

Study Protocol Amendment 3.0 (09 December 2016)

Study Protocol Amendment 4.0 (10 July 2017)

Study Protocol Amendment 5.0 (14 November 2017)

Study Protocol Amendment 6.0: Site Specific – Sites [redacted] and [redacted] (14 November 2018)

Study Protocol Amendment 7.0 (27 September 2019)

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
PROTOCOL NUMBER:	FGCL-3019-079
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	126630
STUDY DRUG:	FG-3019
INDICATION:	Duchenne Muscular Dystrophy
FIBROGEN MEDICAL MONITOR	Name: [redacted] FibroGen, Inc. Title: [redacted] Telephone: [redacted] Mobile/Pager: [redacted] E-mail Address: [redacted]
ORIGINAL PROTOCOL:	16 June 2015

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy

FGCL-3019-079

16 June 2015

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen at the address provided below. Please retain the original for your study files.

[redacted]
FibroGen, Inc.
409 Illinois Street
San Francisco, California 94158 USA

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 16 June 2015

This protocol is approved by FibroGen.

[redacted]

FibroGen Inc.

6/19/2015

Date

PROTOCOL SYNOPSIS

Study Title:	Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
Protocol Number:	FGCL-3019-079
Investigational Product:	FG-3019 (Recombinant fully human IgG_1 kappa monoclonal antibody to connective tissue growth factor)
Study Phase:	Phase 2
Target Population:	Non-ambulatory subjects with Duchenne Muscular Dystrophy (DMD)
Number of Subjects Planned:	22
Study Centers Planned:	Up to 10 centers

OBJECTIVES

Primary Objective

To estimate FG-3019's efficacy in non-ambulatory subjects with DMD

Secondary Objectives

1. To evaluate safety and tolerability of FG-3019 administered intravenously every 2 weeks
2. To assess pharmacokinetics of FG-3019
3. To evaluate pharmacodynamic markers of FG-3019's effects in DMD

ENDPOINTS/ASSESSMENTS

Efficacy

Primary Endpoint

- Difference in annual FVC (% predicted) decline during treatment of FG-3019 compared with the estimated annual decline prior to FG-3019 treatment.

Secondary Endpoints

- Change from baseline to 1 year in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory

flow (PEF), peak cough flow

- Change in LVEF from Baseline to 1 year
- Change from baseline to 1 year in Performance of Upper Limb (PUL) Score
- Change from baseline to 1 year in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to 1 year in cardiac fibrosis score assessed by MRI
- Change from baseline to 1 year in forearm muscle fat and fibrosis assessed by MRI
- Changes from baseline to 2 years in the efficacy parameters

Exploratory, Pharmacokinetics, Pharmacodynamics

- Pharmacokinetic (PK) profile of FG-3019 (including C_{min}, C_{max}, AUC(tau), and $t_{1/2}$)
  - In the overall population
  - In subjects 12 to 16 years of age, inclusive
  - In subjects older than 16 years
  - Comparison of PK profiles across age groups
- Plasma CTGF
- Creatine kinase (CK)
- Circulating biomarkers
- Effect of concomitant corticosteroid treatment on LVEF and cardiac fibrosis

Safety

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, and discontinuation of treatment for treatment-related AEs in different treatment arms

STUDY DESIGN

This study will be an open-label, single arm study of up to 22 subjects. Each subject will receive FG-3019 (35 mg/kg, every 2 weeks) for 2 years. All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow). An interim analysis of safety and efficacy will be performed after all evaluable subjects complete one year of dosing.

If this analysis indicates a potential benefit, the study will be continued through Week 112 to determine the further course of any trends in efficacy and safety parameters observed after 52 weeks of treatment.

STUDY PROCEDURES

Details regarding study procedures are provided as follows:

Appendix 1: Screening Period through Week 26

Appendix 2: Week 28 through Week 52

Appendix 3: Year 2 and Posttreatment

Appendix 4: Pharmacokinetic and Pharmacodynamic Sampling Times

MAIN SELECTION CRITERIA

Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory (wheelchair dependent)
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (forearm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. Estimated annual decline of FVC (% predicted) of ≥5% based upon at least 2 PFTs done in the previous 18 months, in addition to the screening FVC.
10. Left ventricular ejection fraction >45%
11. Stable regimen of heart failure cardiac medications (e,g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) for at least 6 weeks prior to screening
12. Meets one of the following criteria regarding corticosteroid use:
    a. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation.
    or
    b. No use of corticosteroids for at least 6 months before screening and willingness to abstain from corticosteroid use for the duration of study participation.
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >10 g/dL
    c. Absolute neutrophil count >1000/mcL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤2x upper limit of normal (ULN)

c. Total bilirubin ≤1.5xULN

17. If sexually active, will use medically accepted contraceptives during participation in the study.

Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 2 years of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated back surgery within 1 year
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 6 weeks prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 6 weeks
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 or weight >117 kg
10. Exposure to another investigational drug within 28 days prior to start of study treatment
11. Ongoing participation in any other therapeutic clinical trial

TREATMENTS

FG-3019 Dose, and Mode of Administration

Each subject will receive FG-3019 (35 mg/kg, every 2 weeks) for 2 years. The dose of FG-3019 (35 mg/kg) for each infusion should be based on body weight obtained during screening. If a subject has a weight change of more than 10%, the total FG-3019 dose will be adjusted based on the new weight.

Reference Therapy: Not applicable

Concomitant Medications/Therapies: Subjects will receive full supportive care as required by their clinical condition. Concomitant use of corticosteroids is allowed provided subjects were receiving steroids for at least 6 months and were receiving a stable dose for at least 3 months prior to the first dose of FG-3019. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for Duchenne patients receiving glucocorticoid therapy. Investigational agents and currently investigational agents that receive marketing authorization during this trial are prohibited. Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

STATISTIC METHODS

This study will enroll up to 22 subjects. A sample size of 22 subjects will provide 84% power to detect an absolute difference of 3.5% in FVC % predicted, using a two-sided, one-sample paired t-test to compare the annual change posttreatment with that prior to treatment at significance level 0.05. This calculation is based on assumption of standard deviation of 5% and assumption of two dropouts without any efficacy assessments at study completion.

The primary basis for assessment of efficacy will be the capacity of FG-3019 to reduce the rate of deterioration of FVC. The primary endpoint is the difference in annual FVC (% predicted) decline during treatment with FG-3019 compared with the annual decline prior to treatment with FG-3019. The posttreatment annual change in FVC (% predicted) will be compared to that prior to treatment using a mixed effect repeated measures model (MMRM), with adjustment of baseline FVC % predicted and use of corticosteroid. Effect of age (≤16 versus >16) and effect of disease characteristics at baseline, such as time since loss of ambulation, use of ventilation, spine surgery, type of genetic mutation, will be evaluated and may be included in analysis models as appropriate. The difference in annual decline rate will be presented in two-sided 95% confidence interval. Two-sided test on whether the difference is significantly different from zero will be reported.

The analysis of the primary endpoint will be based on the Full Analysis Set population. For subjects who drop out of the study early, their annual change in FVC % predicted will be estimated via the combination of available assessments and the MMRM model.

Change from baseline to one year and to two years in FVC (% predicted) will be estimated via the above mentioned MMRM model. If a substantial number of subjects drop out of the study before entering Year 2 treatment, change from baseline to 2 years will be estimated only for the subset of subjects who have provided Year 2 efficacy assessment.

Summary statistics for observed values, change from baseline, and percent change from baseline will be reported for all secondary endpoints. For those secondary outcomes where historical data is available, the effect of FG-3019 may be investigated further by performing repeated measures analyses.

FG-3019 concentrations and derived PK parameters will be tabulated and summarized using descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters. Attainment of steady-state will be investigated.

Safety analyses will include summary of adverse events (including treatment emergent AEs, treatment emergent serious AEs, deaths, and infusion-associated AEs), prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs), and physical exams.

TABLE OF CONTENTS

LIST OF APPENDICES

2 BACKGROUND

2.1 Description of FG-3019

FG-3019 is a recombinant fully human immunoglobulin G_1 (IgG) kappa monoclonal antibody to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role. These diseases include liver fibrosis due to hepatitis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne Muscular Dystrophy (DMD). FG-3019 (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. FG-3019 contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2 Duchenne Muscle Dystrophy

Duchenne muscular dystrophy (DMD) is usually inherited in an X-linked recessive fashion, but it can occur as a result of spontaneous mutation in boys from families without a known history of the condition. On the basis of some 40 studies including several million male births, incidence at birth of Duchenne muscular dystrophy is around 1:3300, and its prevalence in the population (in terms of the total male population) is around 1:16500 (Emery, 1991).

DMD is a result of mutations (mainly deletions) in the dystrophin gene (DMD; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration with loss of independent ambulation by the age of 13 years (Bushby, 2010).

In skeletal muscles of DMD patients constant myofiber breakdown results in persistent activation of myofibroblasts and altered production of extracellular matrix (ECM) resulting in extensive fibrosis. Muscle fibrosis is the only myo-pathologic parameter that significantly correlated with poor motor outcome as assessed by quadriceps muscle strength, manual muscle testing of upper and lower limbs, and age at ambulation loss (Desguerre, 2009).

Patients with DMD are generally wheelchair bound before they develop significant respiratory muscle weakness. Respiratory complications are the primary cause of morbidity and mortality in DMD as progressive respiratory muscle weakness leads to hypoventilation and/or recurrent atelectasis and pneumonia, secondary to decreased cough effectiveness (McKim, 2012).

After age 10 to 14, patients gradually begin to lose respiratory muscle function based on pulmonary function tests (PFTs) such as forced vital capacity (FVC). The median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001, Tangsrud, 2001).

Because of improvements in respiratory care, cardiac dysfunction is now a leading cause of morbidity and mortality in DMD patients (Schram, 2013). Progressive myocardial fibrosis, as detected by late gadolinium enhancement (LGE), is strongly correlated with the left ventricular ejection fraction (LVEF) decline in Duchenne muscular dystrophy patients. Longer steroid treatment duration is associated with a lower age-related increase in myocardial fibrosis burden (Tandon, 2015).

2.2.1 Relevance of Connective Tissue Growth Factor (CTGF) in DMD

Connective tissue growth factor (CTGF) is a nonstructural regulatory protein present in the extracellular matrix that has an important role in fibrosis. Skeletal muscle from DMD patients, dystrophic dogs, and mdx mice all show elevated levels of CTGF (Sun, 2008).

CTGF can reproduce or amplify the effects of TGFβ on fibrosis by inducing collagen type 1, α5 integrin, and fibronectin much more potently than TGFβ in fibroblasts (Kharraz, 2014).

Comparison of mdx mice with normal or genetically depleted levels of CTGF revealed that exercised mice with reduced CTGF developed less fibrosis and exhibited better muscle strength than mice with normal levels of CTGF (Morales, 2013). In culture, both myoblasts and myotubes were shown to express and secrete CTGF to the medium, and respond to the growth factor by increasing the extracellular matrix constituents, partially inhibiting myoblasts differentiation and inducing myoblasts dedifferentiation (Vial, 2008).

In DMD, the role of CTGF might extend well beyond replacement fibrosis secondary to loss of muscle fibers, since its overexpression in skeletal muscle could by itself induce a dystrophic phenotype (Morales, 2013).

A major feature of the hearts of DMD patients is cardiac fibrosis. Cardiac fibrosis is associated with increased CTGF expression in the *mdx* mouse heart. CTGF may be a key mediator of early and persistent fibrosis in dystrophic cardiomyopathy (Au, 2011).

CTGF is critically involved in several chronic fibro-degenerative diseases. FG-3019 treatment has been shown to positively the affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.

2.3 A Summary of Relevant Findings from Nonclinical Studies and from Clinical Trials

Please refer to the most recent version of FG-3019 Investigator's Brochure.

2.3.1 Nonclinical Studies

In DMD, the genetic loss of the cytoskeletal protein dystrophin results in muscle damage that, leads to progressive replacement of muscle with fibrotic and fat tissue. This progressive muscle damage can be recapitulated in the DMD mouse model (*mdx*), and accelerated by muscle usage (Pessina, 2014).

As was observed with genetic depletion of CTGF, pharmacologic inhibition of active CTGF in *mdx* mice by treatment with FG-3019 resulted in reduced fibrosis and skeletal muscle damage, as well as improved preservation of skeletal muscle strength in isolated muscles. The FG-3019 treated *mdx* mice were also subjected to a test of exercise endurance, in which they showed better performance than *mdx* mice injected with control IgG (Morales, 2013).

FG-3019 treatment of *mdx* mice was associated with decreased skeletal muscle damage and fibrosis, decreased collagen III and fibronectin expression, decreased plasma creatinine kinase (CK) (Morales, 2013), and increased isometric force of skeletal muscle (Morales, 2011).

2.3.2 Pharmacokinetics

Key findings are summarized below from Phase 1 and 2 studies investigating the pharmacokinetics (PK) of FG-3019 in subjects with diabetic kidney disease, idiopathic pulmonary fibrosis, and pancreatic cancer:

- FG-3019 was administered over the dose range of 3 to 45 mg/kg every 2 weeks and 17.5 to 22.5 mg/kg weekly.
- FG-3019 exposure (eg, mean/median C_{max} and C_{min}, area under the curve [AUC]) generally increased with increasing dose.
- The $t_{1/2}$ was approximately 1 to 2 weeks at doses >25 mg/kg in a trial in pancreatic cancer subjects.

2.3.3 Safety

Key findings are summarized below from the Phase 1 and 2 studies involving more than 400 adults with diabetic kidney disease, idiopathic pulmonary fibrosis, and liver fibrosis due to hepatitis B or pancreatic cancer:

- Overall, FG-3019 was well tolerated across the range of doses noted above, and there were no dose-limiting toxicities.
- Treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity and transient in duration.
- Infusion-related reactions have been mild-to-moderate and did not recur following re-administration of FG-3019
- TEAEs were considered typical of the subjects' underlying medical condition(s) and, in the placebo-controlled studies, were equally distributed between placebo and FG-3019 treatment groups.
- No apparent pattern to TEAEs that occurred within 24 hours after infusions was observed.
- No apparent pattern for treatment-emergent serious adverse events (TESAEs) was observed during clinical testing.

2.3.4 Efficacy

Key efficacy findings are summarized below from the Phase 1 and 2 studies of CTGF inhibition by FG-3019 in indications other than DMD.

2.3.4.1 Pancreatic Cancer

Biweekly doses of up to and including 45 mg/kg and weekly doses of 17.5 and 22.5 mg/kg were administered to subjects with previously untreated locally advanced or metastatic pancreatic adenocarcinoma. Increased exposure to FG-3019 was associated with increased survival. There appears to be a relationship between survival and trough blood levels of FG-3019 (C_{min}). Notably C_{min} >150 mcg/mL after the first dose of FG-3019 (Day 15) was associated with significantly increased progression free survival and overall survival.

A maximal effect in survival benefit was achieved at dose levels of 25 to 45 mg/kg/2 weeks.

2.3.4.2 Idiopathic Pulmonary Fibrosis (IPF)

In subjects with IPF who completed 45 weeks of dosing with 15 or 30 mg/kg FG-3019, approximately 40% of subjects had stable or improved lung fibrosis by quantitative high resolution CT imaging compared to baseline values with approximately 30% having improved pulmonary fibrosis.

Overall, subjects with stable or improved lung fibrosis also had stable or improved FVC (% predicted).

2.4 Risks and Benefits

FG-3019 has been generally well tolerated with most adverse events being typical of those expected for subjects with the underlying disease conditions.

Infusion-related reactions have been rarely observed in some subjects treated with FG-3019. Across studies in other indications, infusion-related reactions have been mild-to-moderate did not result in discontinuation of treatment with FG-3019, and did not result in the use of prophylaxis for subsequent infusions.

The favorable experience with FG-3019 to date does not exclude the possibility of more severe infusion reactions occurring in future subjects.

This is the first clinical study of FG-3019 in DMD. There are currently no confirmed benefits to subjects with DMD treated with FG-3019. However, a potential benefit of treatment with FG-3019 is indicated in preclinical models of DMD and previous clinical studies of FG-3019 in other indications where CTGF is also associated with disease progression.

Dose regimen equal to or exceeding 35 mg/kg have been implemented in other indications in adult subjects. The objective of these studies was to inhibit bioactive CTGF, which is associated with disease progression in a number of indications. Please refer to the Investigator's Brochure for a comprehensive summary of efficacy, safety, and exposure data.

The current study will explore the clinical relevance of CTGF inhibition, as indicated in preclinical models, in DMD patients.

2.5 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Periods

FG-3019 is administered as an IV infusion at a dose of 35 mg/kg every two weeks for two years (Week 0 to Week 102). The dose, frequency and route of administration correspond with dose regimens that were well tolerated and possibly associated with efficacy in clinical studies in adults with IPF and pancreatic cancer. In both of these indications FG-3019 was administered at doses that included the targeted dose regimen for the current study (35 mg/kg bodyweight) and greater (45 mg/kg bodyweight). These doses were not associated with dose limiting toxicity.

The overall objective of all of these studies, including the current study, is to provide a dose associated with clinically relevant CTGF blockade to impede progression of serious disease states. Body weight-related dosing and utilization of a dose no greater than the maximal dose used in adults are expected to ensure that systemic exposure in the targeted pediatric population will not exceed the systemic exposure achieved in adults.

PK assessments will be done during the course of the study and facilitate ongoing monitoring of exposure to FG-3019 during the course of the study.

The planned treatment duration is no longer than total treatment periods achieved in previous studies with FG-3019.

The duration of treatment of the current study is also similar to the duration of other studies in DMD and is expected to provide sufficient basis to evaluate potential benefit in the targeted pediatric population with DMD.

2.6 Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents. Detailed information regarding study conduct is found in Sections 10, 11, 12, and 13.

2.7 Population to be Studied

Non-ambulatory adolescents and adults with DMD will be enrolled in this trial.
A detailed inclusion/exclusion list is provided in Section 5.

3 OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is to estimate FG-3019's efficacy in non-ambulatory subjects with DMD.

3.2 Secondary Objectives

The following are the secondary objectives of this trial:

1. To evaluate safety and tolerability of FG-3019 administered intravenously every 2 weeks
2. To assess pharmacokinetics of FG-3019 in the targeted pediatric population
3. To evaluate pharmacodynamic markers of FG-3019's effects in DMD

4 STUDY DESIGN

4.1 Endpoints and Assessments

4.1.1 Primary Endpoint

The primary endpoint is the difference in annual forced vital capacity (FVC) (% predicted) decline during treatment of FG-3019 compared with the estimated annual decline prior to FG-3019 treatment.

4.1.2 Secondary Endpoints

The following are the secondary endpoints:

- Change from baseline to 1 year in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow
- Change in LVEF from baseline to 1 year
- Change from baseline to 1 year in Performance of Upper Limb (PUL) Score
- Change from baseline to 1 year in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to 1 year in cardiac fibrosis score assessed by MRI
- Change from baseline to 1 year in forearm muscle fat and fibrosis assessed by MRI
- Changes from baseline to 2 years in the efficacy parameters

4.1.3 Exploratory, Pharmacokinetic and Pharmacodynamic Outcome Measures

Exploratory outcome measures for this trial are:

- Pharmacokinetic (PK) profile of FG-3019 (including C_{min}, C_{max}, AUC(tau), and $t_{1/2}$)
    - In the overall population
    - In subjects 12 to 16 years of age, inclusive
    - In subjects older than 16 years
    - Comparison of PK profiles across age groups
- Plasma and urine CTGF
- Creatine kinase (CK)
- Circulating biomarkers
- Effect of concomitant corticosteroid treatment on LVEF and cardiac fibrosis

4.1.4 Safety Assessments

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

4.2 Trial Overview

This study will be an open-label, single arm study of up to 22 subjects. Each subject will receive FG-3019 (35 mg/kg, every 2 weeks) for up to 2 years. All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow) on a continuous basis.

An interim analysis of safety and efficacy will be performed after all evaluable subjects complete one year of dosing. If this analysis indicates a potential positive benefit/risk, the treatment will continue through Week 102 to determine the further course of any trends in efficacy parameters observed after 52 weeks of treatment. Upon completion of treatment or premature discontinuation from the trial, subjects will be asked to return to the investigative site to complete final safety and efficacy assessments 10 weeks after the last dose of FG-3019.

4.3 Study Treatment

4.3.1 Dose and Schedule

Each subject will receive FG-3019 (35 mg/kg) intravenously every 2 weeks (q2w). See Section 6 for detailed information on study drug formulation, storage, and administration.

4.3.2 Rationale for Dose and Schedule

The FG-3019 dose is based on results of a study in adult subjects with pancreatic cancer. In that study (Section 2.3.4.1), minimum FG-3019 blood levels (C_{min}) ≥150 mcg/mL were associated with increased median survival and 1 year survival compared to subjects with C_{min} <150 mcg/mL. Given the apparent threshold effect for increased benefit when minimal FG-3019 exposure is ≥150 mcg/mL and based on PK analysis using these data, the planned dose of 35 mg/kg administered every 2 weeks is projected to achieve this minimum exposure in the targeted DMD study population.

4.4 Concomitant Medications, Procedures and Nondrug Therapies

Subjects will receive full supportive care as required by their clinical condition. Concomitant use of corticosteroids is allowed provided that subjects were receiving steroids for at least 6 months and were receiving a stable dose for at least 3 months prior to the first dose of FG-3019. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy.

Investigational agents and currently investigational agents that receive marketing authorization during this trial are prohibited.

Concomitant medications (any prescription and/or over-the-counter [OTC] preparation) and procedures or nondrug therapies (e.g., physical therapy or acupuncture) used by a subject while participating in this clinical trial must be recorded from the Screening Visit through the End-of-Study Visit.

Questions regarding potential impact of concomitant medications on evaluability of subjects enrolled in the study should be addressed to the attention of the FibroGen Medical Monitor or designee.

4.4.1 Contraception

Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy of a partner must be reported (Section 8.3.6).

4.5 Safety Plan

An ongoing safety review is facilitated by the unblinded nature of the study. FibroGen will review safety data and will communicate the results of these reviews to investigators by email or teleconference on a regular basis. In addition, FibroGen will review safety experience with investigators during teleconferences that will be held at least quarterly and include the conclusions of the Data Monitoring Committee's (DMC) latest data review.

FibroGen will notify investigators immediately if a new safety risk is identified.

4.6 Data Monitoring Committee

A DMC will be utilized and will be composed of external and internal (FibroGen) experts. Composition and responsibilities of the DMC are defined in a separate DMC charter.

DMC responsibilities include review of safety data, available pharmacokinetic data, and pulmonary function tests.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory (wheelchair dependent)
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (forearm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. Estimated annual decline of FVC (% predicted) of ≥5% based upon at least 2 PFTs done in the previous 18 months, in addition to the screening FVC.
10. Left ventricular ejection fraction >45%
11. Stable regimen of heart failure cardiac medications (e,g, angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) for at least 6 weeks prior to screening
12. Meets one of the following criteria regarding corticosteroid use:
    a. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation.

       or

    b. No use of corticosteroids for at least 6 months before screening and willingness to abstain from corticosteroid use for the duration of study participation.
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >10 g/dL
    c. Absolute neutrophil count >1000/mcL

16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤2x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study.

5.2 Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 2 years of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated back surgery within 1 year
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 6 weeks prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 6 weeks
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 or weight >117 kg
10. Exposure to another investigational drug within 28 days prior to start of study treatment
11. Ongoing participation in any other therapeutic clinical trial

5.3 Subject Withdrawal

Subjects may withdraw from the study at any time.

The investigator will remove a subject from study treatment for the following reasons:

- Adverse events, which in the opinion of the Principal Investigator and/or FibroGen preclude further study drug dosing
- Nonadherence to protocol-defined procedures, in particular missing of 3 or more sequential study drug infusions
- Not available for safety assessments

Subjects who discontinue the study early should be strongly encouraged to complete the evaluations described in Section 7.1.3.

5.4 Replacement of Subjects

Subjects may be replaced in this study if a subject's participation is not terminated due to safety or tolerability issues and is replaced prior to completion of targeted recruitment of 22 subjects into the study. Replacement decisions will be made between the sponsor and investigator on a case-by-case basis.

5.5 Study Termination

This trial can be terminated by the sponsor at any time for any reason.

6 STUDY DRUG/TREATMENT SUPPLY

6.1 FibroGen Investigational Product

FG-3019 is a fully human IgG_1 kappa monoclonal antibody that binds to CTGF.

6.1.1 Formulation

FG-3019 is supplied in single-use glass vials containing 10 mL of a sterile, preservative-free solution. The solution is composed of 10 mg/mL FG-3019, 1.60 mg/mL l-histidine, 3.08 mg/mL l-histidine HCl, 8.01 mg/mL sodium chloride and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0.

6.1.2 Storage

Vials of FG-3019 must be stored refrigerated (2°C to 8°C), temperature-controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation.

6.1.3 Preparation of Dose for Administration

The dose of FG-3019 (35 mg/kg) for each infusion should be based on body weight obtained during screening. If a subject has a weight change of more than 10%, the total FG-3019 dose will be adjusted based on the new weight. FG-3109 may be administered undiluted or, for convenience of infusion, may be diluted with 0.9% Sodium Chloride Injection according to the Dose Preparation Instructions in the Study Reference Investigational Product (IP) Manual.

FG-3019 will be administered as soon as possible after release from the site's pharmacy and within 24 hours of preparation. FG-3019 will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

6.1.4 Administration

Agent	Dose	Route	Schedule
FG-3019	35 mg/kg	IV, over 1 hour	q 2 weeks
DO NOT ADMINISTER FG-3019 AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.			

Subjects should be carefully monitored for reaction during the first infusion with a physician available as needed. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation for the initial 3 infusions. The IV access should remain in place and maintained per site procedures until the end of this posttreatment observation period. If a subject does not have an infusion reaction (Section 8.2.3) during 3 consecutive infusions, the infusion duration may be shortened to as little as 30 minutes provided the Investigator thinks infusing this fluid load is safe. The post-infusion observation period will remain as 1 hour.

If a subject has an infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences an infusion reaction and continues FG-3019 dosing, a physician must be immediately available during subsequent infusions and observation periods until the subject does not have any infusion reaction for three sequential infusions.

Premedication, such as antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are not normally administered before infusions of FG-3019. Premedication may be used for subjects who experience infusion reactions at the discretion of the investigator after discussion with the Medical Monitor.

FG-3019 will be administered in a hospital or ambulatory setting with adequate facilities for managing medical emergencies for at least three infusions to confirm the subject does not have an infusion reaction. The study site must have trained staff and medications for the treatment of acute reactions, including anaphylaxis, immediately available. There is no specific treatment for an FG-3019 overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

7 ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

7.1 Study Procedures by Visit

All study procedures and assessments will be performed in accordance with the Schedule of Assessments presented in Appendix 1 (Screening Period through Week 26), Appendix 2 (Weeks 28 through 52), Appendix 3 (second year of treatment), and Appendix 4 (Pharmacokinetic Sampling Times).

For all potential subjects, screening procedures required to determine subject eligibility will be performed within 28 days prior to Day 0 (first infusion of FG-3019). Potential subjects may be re-screened if initial screening procedures lie outside the 28-day screening period prior to planned study entry.

Subject's eligibility for this study will be reviewed and approved by Sponsor's medical monitor prior to subject enrollment.

The following assessments are relevant to the assessment of efficacy: pulmonary function tests (FVC, mean inspiratory flow (MIF), peak expiratory flow), Brooke Upper Extremity Rating Scale, Performance of the Upper Limb, pinch strength, grip strength, cardiac MRI, and muscle MRI. Refer to the Study Reference Manual for details.

Approved windows for performing study assessments are defined in the following sections.

7.1.1 Screening Period (no earlier than Day -28)

Assessments to be conducted during the screening period are presented in Appendix 1.

Screening assessments may be completed over several visits during the screening period. It is recommended that the less invasive screening assessments be performed first upon completion of the signed Informed Consent and/or Assent Form [ICF] (demographics, medical history, blood draws, electrocardiogram [ECG], vitals (includes body weight and height), physical exam, pulmonary function tests (PFTs), and then followed by the more rigorous screening assessments (i.e., muscle function tests, cardiac MRI).

A cardiac MRI performed within 3 months prior to Day 0 (day of dosing) is acceptable to confirm eligibility based on the LVEF study entry criterion and as baseline cardiac MRI. If this historic MRI is not available, a cardiac MRI must be performed during the Screening Period.

A forearm muscle MRI may be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Muscle and pulmonary function tests (PFTs) will be performed during the screening period. Muscle function and PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both timepoints will be used to establish baseline values.

In addition, an exploratory blood sample will be drawn for analysis of circulating biomarkers of fibrosis and specific muscle miRNAs (dystromirs) prior to first initial FG-3019 infusion.

7.1.2 Dosing Period

The dosing period begins on the first day of dosing with study treatment (Week 0) and continues through Week 102. Subjects will receive study drug every 2 weeks.

The visit window for all dosing visits is ±2 days.

Assessments and procedures to be performed during the dosing period are presented in Appendix 1 (Screening Period through Week 26), Appendix 2 (Weeks 28 through 52), and Appendix 3 (second year of treatment and posttreatment).

Muscle or pulmonary function tests that cannot be performed or produce inadequate results during a specified visit should be performed by the next scheduled dosing visit.

Both cardiac and muscle MRIs may be performed within ±2 weeks of the specific visit.

Blood samples will be drawn for pharmacokinetic analysis according to the schedule in Appendix 4. Blood draws to be collected on non-dosing days may be collected within ±1 or 2 days as outlined in Appendix 4.

7.1.3 End of Treatment (Per-Protocol)

Assessments and procedures to be conducted after the last dose are presented in Appendix 3.

The end of treatment cardiac and muscle MRIs may be performed anytime from Week 104 and Week 112.

7.1.4 Early Withdrawal from Treatment

Subjects who prematurely discontinue the study should be strongly encouraged complete the safety and efficacy evaluations scheduled for Week 104. All subjects should be encouraged to undergo follow-up 10 weeks (±7 days) after the last dose of FG-3019 for evaluation of adverse events.

7.1.5 Follow-Up Period

The follow-up period begins after subjects have Year 2 efficacy evaluations done at Week 104, or at premature study termination, and is completed 10 weeks (±7 days) after the last dose of FG-3019.

7.1.6 Missed Visits

Every attempt must be made to complete all study visits as outlined in the Schedules of Assessments. Missed infusions will not be replaced. If a subject misses a scheduled efficacy assessment, the assessment should be performed as soon after the missed visit as feasible.

7.1.7 Unscheduled Visits

Unscheduled Visit assessments may be required at the discretion of the investigator.

7.2 Assessments

Please refer to the Schedules of Assessments (Appendix 1, Appendix 2, Appendix 3, and Appendix 4) for the scope and timing of assessments. Please refer to the Laboratory

Manual for details regarding laboratory sample collection and processing; and the Study Reference Manual for details regarding the conduct of functional tests and MRIs.

7.2.1 Pulmonary Function Tests

The following pulmonary function tests (PFTs) will be performed to assess changes in lung function: forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow rate (PEF; PEFR), forced expiratory volume in 1 second (FEV1), and peak cough flow (Mayer, 2015, Miller, 2005).

7.2.2 Muscle Strength and Functional Measurements

The following assessments will be performed to assess changes in upper extremity strength and function: Brooke Upper Extremity Rating Scale (Brooke Scale), Performance of the Upper Limb (PUL), Grip Test, and Pinch Strength Test.

7.2.3 Cardiac MRI

Cardiac MRIs, will be performed at BL and at yearly intervals to assess changes in left ventricular ejection fraction (LVEF) and presence of late gadolinium enhancement (LGE), a marker for myocardial fibrosis.

7.2.4 Forearm MRI

Forearm MRIs will be performed at BL and at yearly intervals to assess changes in degree of fatty replacement of select muscle groups by T2 relaxation time mapping.

7.2.5 Quality of Life Questionnaire

Pediatrics Outcomes Data Collection Instrument (PODCI) Quality Outcome Questionnaire will be performed to assess if treatment with FG-3019 improves quality of life as assessed by this questionnaire.

7.2.6 Vital Signs and Physical Examinations

A physical examination will be performed at screening and baseline, every 12 weeks and at end of treatment and post-treatment follow-up. Examinations in screening, Week 52 (±2 weeks) and Week 104 (±2 weeks) should be complete examinations. Other examinations may be disease-specific or problem-oriented examinations.

Vital signs (pulse, respiration, sitting blood pressure, and temperature) will be collected prior to start of each infusion, within 15 minutes of the end of each infusion, and within 15 minutes of the completion of the post-infusion observation period.

7.2.7 Laboratory Assessments

All laboratory tests of blood and/or urine specimens will be performed at a central laboratory or FibroGen, as appropriate. A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local clinical laboratories will be used to assess and facilitate the management of adverse events and to provide usual standard of care. Local clinical laboratory data will not be collected in the study database except for abnormalities that are reported as adverse events.

7.2.7.1 Safety Assessments

Blood samples will be 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.

7.2.7.1.1 Pharmacokinetics

Plasma concentrations of FG-3019 will be determined on Day 0 pre-dose and within 1 hour post infusion, then on Days 2, 4, 7, 10, and 14. The Day 14 sample should be on the same day of, but prior to the start of next infusion.

Day 2, 4, 7, and 10 PK assessments represent target days following the first dose; however, actual sample collection time of up to ±1 or 2 days of the target time is acceptable as long as the actual time of dosing and actual time of each sample collection are recorded accurately.

At Weeks 26, 52, 78, and 102, trough FG-3019 levels (C_{min}) will be determined prior to study drug infusion.

PK samples will also be drawn within 60 minutes of infusion completion on Weeks 52 and 102.

7.2.7.2 Plasma and Urine CTGF

Plasma and urine samples will be analyzed for CTGF concentrations prior to start of study drug dosing and at study completion.

7.2.7.3 Biomarkers

Blood samples will be drawn for analysis of biomarkers. The exact biomarkers will be based on current scientific knowledge regarding CTGF, FG-3019 and DMD at the time the tests are performed. No genetic testing will be performed.

8 ASSESSMENT OF SAFETY

8.1 Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 1 (Screening Period through Week 26), Appendix 2 (Weeks 28 through 52), and Appendix 3 (second year of treatment). In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the Study Drug.

8.2 Definitions

8.2.1 Definition of an Adverse Event (AE)

For the purpose of this study, an AE is any untoward medical occurrence that occurred in the protocol-specified AE reporting period, and which does not necessarily have a causal relationship with the study drug. An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.3.1).

8.2.2 Definition of a Serious Adverse Event (SAE)

A **serious adverse event** is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.2.3 Definition of an Infusion Reaction

Infusion reactions are immunologic reactions to an infused protein, and are different from events resulting from the process of infusing the protein (e.g., infusion site bruise) and are different from adverse events due to the infused protein's intended or unintended pharmacologic effects.

8.2.3.1 Acute Infusion Reaction

An acute infusion reaction is one that meets both of the following criteria:

1. Occurs during or within 1 hour after infusion; and
2. Clinical manifestations consistent with:
    - IgE-mediated and non-IgE mediated hypersensitivity reactions, including but not limited to urticaria, skin rashes, angioedema, laryngeal edema, bronchospasm, gastrointestinal symptoms and hypotension; or
    - Cytokine release syndrome, including but not limited to fever, respiratory symptoms without the presence of wheezing, tremors, chills, flushing, pruritus, changes in blood pressure, dyspnea, chest discomfort, back pain, nausea, vomiting, diarrhea, and skin rashes.

8.2.3.2 Delayed Infusion Reaction

A delayed infusion reaction is one that meets both of the following criteria:

1. Occurs ≥1 hour after the infusion
2. Clinical manifestations as described above.

8.2.3.3 Reporting Possible and Confirmed Infusion Reactions

Possible and confirmed infusion reactions must be reported in the Infusion Reaction CRF section.

Investigators should complete the Infusion Reaction report and contact the Medical Monitor within the same timeframe as reporting SAEs, even if the infusion reaction is not an SAE. See Study Reference Manual for additional details.

8.2.4 Special Situations

Certain safety events, called 'Special Situations' that occur in association with the study drug(s) include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product

- Inadvertent or accidental exposure to the medicinal product
- Medication error involving the medicinal product (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

Special Situations will be reported to the sponsor or designated vendor within the same timeframe as SAEs on a Medication Error report form.

8.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 6 weeks after the last dose of study drug, except for pregnancy reporting (Section 8.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5).

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever is possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff.

New indications for medications started during the AE reporting period (i.e., after informed consent is obtained until 6 weeks after the last dose of study drug) will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the Investigator to meet the specified criteria.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome

- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

8.3.3 Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 4.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild**: Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; Likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death:** Fatal AE.

8.3.4 Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- **Related:**
    - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re-occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- **Not Related:**
    - The event represents a pre-existing underlying disease that has not worsened on study
    - The event has the same characteristics of a known side-effect associated with a co-medication
    - The event is an anticipated medical condition of anticipated severity for the study population
    - The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5 Reporting Serious Adverse Events on the SAE Report Form

An SAE must be reported to the Sponsor and/or its designated safety management vendor within 24 hours of becoming aware of the SAE.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

The contact information for SAE reporting is as follows:

U.S. Toll-Free Fax Number: [redacted]

Email: [redacted]

8.3.5.1 Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2 Deaths

The investigator will report the fatal or life-threatening event immediately to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to 6 weeks after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. Additionally, the site must complete the appropriate CRF page.

8.3.6 Pregnancies: Reporting and Follow-up of Subjects

The outcome of all pregnancies should be followed up and documented as described. Consent must be obtained from male subject's partner to collect information related to the pregnancy and outcome (and will be handled on a case-by-case basis with IRB/IEC approval). A Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

8.3.7 Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all laboratory results throughout the study in a timely manner, and determine whether any abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

8.3.8 Risk Management/Monitoring Programs

No specific risk management programs will be implemented.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

This study will enroll up to 22 subjects. This sample size will provide 84% power to detect an absolute difference of 3.5% in FVC % predicted, using a two-sided, one-sample paired t-test to compare the annual change posttreatment with that prior to treatment at a significance level of 0.05. This calculation is based on assumption of standard deviation of 5% and assumption of two dropouts without any efficacy assessments.

9.2 Analysis Populations

9.2.1 Safety Population

The Safety Population will consist of all subjects who have received any dose of FG-3019.

9.2.2 Full Analysis Set Population

The Full Analysis Set Population will consist of all subjects in the Safety Population who have at least one post-baseline FVC assessment.

9.3 Statistical Analysis

9.3.1 General Considerations

Baseline values are values obtained during the screening period or during the windows specified for individual tests. Consequently, baseline values may include results of tests performed before the specified screening period (e.g., cardiac MRI) or results of tests performed after the specified screening period (e.g., muscle MRI). The Statistical Analysis Plan will provide details for baseline values for each test.

Baseline characteristics, safety, efficacy, pharmacokinetic and pharmacodynamic parameters will be summarized descriptively based on available data in the Safety Population. Continuous variables will be reported using n, mean, standard deviation or standard error, median, minimum, and maximum; categorical variables will be by frequency count and percentage of subjects in each category of the variable. Analyses of the primary efficacy endpoint will be based on the Full Analysis Set Population. Two-sided 95% confidence intervals will be presented for key efficacy parameters and two-sided 90% confidence intervals for PK parameters. All statistical tests will be performed at an α=0.05 level of significance, using two-sided tests, unless otherwise stated. Assessments as well as derived parameters will be presented in data listings for all subjects in the Safety Population.

9.3.2 Subject Enrollment and Disposition

The number of subjects in each study population as well as subject completion status and reasons for early discontinuation will be summarized.

9.3.3 Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized. Baseline disease characteristics include age when subject became non-ambulatory, use of corticosteroids (for current users: years of use; for ex-users: years of use and years since stopped),

ventilation (none, nighttime use, continuous use), spine surgery and years since spine surgery, genetic characteristics (exonic deletion, duplication, point mutation), and other additional information collected during screening. Baseline efficacy measures include PFT parameters, hand and arm functions, cardiac and forearm MRI parameters, and quality of life parameters.

9.4 Efficacy Analyses

9.4.1 Primary Endpoint

The primary basis for assessment of efficacy will be the capacity of FG-3019 to reduce the rate of deterioration of FVC. The primary endpoint is the difference in annual FVC (% predicted) decline during treatment with FG-3019 compared with the annual decline prior to treatment with FG-3019. The posttreatment annual change in FVC (% predicted) will be compared to that prior to treatment using a mixed effect repeated measures model (MMRM), with adjustment of baseline FVC % predicted and use of corticosteroid. Effect of age (≤16 versus >16) and effect of disease characteristics at baseline, such as time since loss of ambulation, use of ventilation, spine surgery, type of genetic mutation, will be evaluated and may be included in analysis models as appropriate. The difference in annual decline rate will be presented in two-sided 95% confidence interval. Two-sided test on whether the difference is significantly from zero will be reported.

The analysis of the primary endpoint will be based on the Full Analysis Set population. For subjects who drop out of the study early, their annual change in FVC % predicted will be estimated via the combination of available assessments and the MMRM model.

Change from baseline to one year and to two years in FVC (% predicted) will be estimated via the above mentioned MMRM model. If a substantial number of subjects drop out of the study before entering Year 2 treatment, change from baseline to 2 years will be estimated only for the subset of subjects who have provided Year 2 efficacy assessment.

9.4.2 Analyses of Other PFT Parameters

Changes from baseline to 1 year and 2 years in other PFT parameters will be estimated via the above MMRM model.

9.4.3 Analysis of PUL Parameters, Pinch and Grip Strength, Brooke Scale

Change from baseline to one year and to two years in hand/arm function and strength will be estimated using the MMRM model with dominant/non-dominant side as a fixed effect and baseline value and other relevant variables as covariates. In order to evaluate overall effect, composite scores may be explored. Two-sided 95% confidence intervals will be presented.

9.4.4 Analysis of LVEF, Cardiac Fibrosis, and Forearm Fat and Fibrosis

Changes from baseline in LVEF, cardiac fibrosis, and forearm fat and fibrosis will be summarized descriptively based on available data at Year 1 and at Year 2.

9.4.5 Analysis of PODCI Quality Outcome Data

Changes from baseline in modified PODCI scores of adolescent subjects and their caregivers will be summarized descriptively based on available data at Year 1 and at Year 2. The data of adult subjects and their caregivers will be summarized separately.

9.4.6 Examination of Subgroups

Comparisons in efficacy parameters between the following subgroups may be performed. Depending on enrollment in each subgroup, grouping may be adjusted to have relatively balanced sizes.

- Age ≤16 versus age >16
- Use of corticosteroids for at least 6 months during the first year of the study versus others
- Spine surgery: yes versus no
- Different genetic characteristics
- Above and below median in years of wheel-chair bound
- Above versus below median of the baseline FVC (% predicted)
- Above versus below median of the hand and arm functional scale
- Above versus below median of the day 15 and the 6-month PK C_{min} levels
- Above versus below median of the baseline CTGF level

9.4.7 Pharmacokinetic and Pharmacodynamic Analyses

FG-3019 concentrations and derived PK parameters (including C_{min}, C_{max}, AUC(tau), and $t_{1/2}$) will be summarized using descriptive statistics. Pharmacokinetic analysis will be performed using commercial software such as WinNonlin.

Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters (1) in the overall population; (2) in subjects 12 to 16 years of age; and (3) in subjects older than 16 years. Comparison of PK parameters between the age groups will be performed. Trough values, measured at several time points during the course of the study, will be compared to determine steady state and accumulation.

9.4.8 Safety Analyses

Safety analyses will include summary of adverse events, prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs), and physical exams. In general, safety data will only be summarized descriptively and no inferential statistical procedures will be applied.

Treatment-emergent adverse events (TEAEs) will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. AEs and SAEs leading to study or treatment discontinuation, infusion reactions, SAEs, and deaths will be listed or tabulated separately.

Clinically significant changes from baseline in vital signs, laboratory tests, physical examinations, and ECG will be identified. Shift tables will summarize changes in selected laboratory measures.

All safety analyses will be performed using data from the Safety Population.

9.5 Interim and Administrative Analyses

In this open-label exploratory study, safety will be monitored on an ongoing basis and efficacy data will be evaluated periodically.

In addition to the above, a full review of efficacy and safety will be performed when PFT and other efficacy data up to and including Week 52 are available for all subjects. The study may be terminated if this review indicates that safety and efficacy endpoints will not be met after two years of treatment.

In addition, the DMC will review trends in PFTs and all other efficacy and safety data in accordance with the DMC charter.

9.6 Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will include detailed plans for presenting and analyzing study data, as well as documentation of changes in protocol-specified analysis plans. The SAP will describe additional study endpoints that are of interest.

10 DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the International Conference on Harmonisation (ICH) E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IVRS [or IWRS], clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The investigator must also permit the U.S. FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the investigator is notified of an inspection pertaining to this study by the U.S. FDA or other applicable regulatory authorities, the investigator must notify FibroGen immediately.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents

11.2 Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

11.3 Database Audit

A database audit will be conducted to ensure data quality and integrity.

12 ETHICS

12.1 Ethical Considerations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

12.2 Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

12.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent (ICF) and/or Assent Form from the subject or written Informed Consent Form signed by the subject's legally authorized representative, as applicable. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

12.4 Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

13 DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs/eCRFs and resolved queries.

13.2 Data Collection, Handling, and Verification

All required data will either be entered onto CRFs/eCRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with a full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion, ensuring that all data is verifiable with source documents.

14 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate document.

15 PUBLICATION POLICY

A detailed explanation of FibroGen's publication policy is described in the Clinical Trial Agreement.

16 REFERENCES

Au CG, Butler TL, Sherwood MC, Egan JR, North KN, Winlaw DS (2011) Increased connective tissue growth factor associated with cardiac fibrosis in the *mdx* mouse model of dystrophic cardiomyopathy. Int J Exp Pathol 92: (1):57-65

Bushby K, Finkel R, Birnkrant DJ, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 9: (1):77-93

Desguerre I, Mayer M, Leturcq F, Barbet JP, Gherardi RK, Christov C (2009) Endomysial fibrosis in Duchenne muscular dystrophy: a marker of poor outcome associated with macrophage alternative activation. J Neuropathol Exp Neurol 68: (7):762-773

Emery AE (1991) Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord 1: (1):19-29

Forbes SC, Willcocks RJ, Triplett WT, et al. (2014) Magnetic resonance imaging and spectroscopy assessment of lower extremity skeletal muscles in boys with Duchenne muscular dystrophy: A multicenter cross sectional study. PLoS ONE **9:** (9):e106435

Kharraz Y, Guerra J, Pessina P, Serrano AL, Munoz-Canoves P (2014) Understanding the process of fibrosis in Duchenne muscular dystrophy. Biomed Res Int **2014:**965631

Mayer OH, Finkel RS, Rummey C, et al. (2015) Characterization of pulmonary function in Duchenne Muscular Dystrophy. Pediatr Pulmonol 50: (5):487-494

McKim DA, Katz SL, Barrowman N, Ni A, LeBlanc C (2012) Lung volume recruitment slows pulmonary function decline in Duchenne muscular dystrophy. Archives of Physical Medicine and Rehabilitation 93: (7):1117-1122

Miller MR, Hankinson J, Brusasco V, et al. (2005) Standardisation of spirometry. Eur Respir J 26: (2):319-338

Morales MG, Cabello-Verrugio C, Santander C, Cabrera D, Goldschmeding R, Brandan E (2011) CTGF/CCN-2 over-expression can directly induce features of skeletal muscle dystrophy. J Pathol 225: (4):490-501

Morales MG, Gutierrez J, Cabello-Verrugio C, et al. (2013) Reducing CTGF/CCN2 slows down *mdx* muscle dystrophy and improves cell therapy. Hum Mol Genet 22: (24):4938-4951

Pessina P, Cabrera D, Morales MG, et al. (2014) Novel and optimized strategies for inducing fibrosis in vivo: Focus on Duchenne Muscular Dystrophy. Skelet Muscle 4:7

Phillips MF, Quinlivan RC, Edwards RH, Calverley PM (2001) Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med 164: (12):2191-2194

Schram G, Fournier A, Leduc H, et al. (2013) All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 61: (9):948-954

Sun G, Haginoya K, Wu Y, et al. (2008) Connective tissue growth factor is overexpressed in muscles of human muscular dystrophy. J Neurol Sci 267: (1-2):48-56

Tandon A, Villa CR, Hor KN, et al. (2015) Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. J Am Heart Assoc 4: (4):e001338

Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH (2001) Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. Arch Dis Child 84: (6):521-524

Vial C, Zuniga LM, Cabello-Verrugio C, Canon P, Fadic R, Brandan E (2008) Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. Journal of Cellular Physiology 215: (2):410-421

Willcocks RJ, Arpan IA, Forbes SC, et al. (2014) Longitudinal measurements of MRI-T2 in boys with Duchenne muscular dystrophy: effects of age and disease progression. Neuromuscul Disord **24:** (5):393-401

17 APPENDICES

Appendix 1 Schedule of Assessments: First Year of Treatment (Screening Period through Week 26)

Assessment[a]	Screening Period (4 Weeks)	Treatment Period (Weeks)													
		0	2	4	6	8	10	12	14	16	18	20	22	24	26
Informed Consent & Assent	X														
Inclusion/ Exclusion	X														
Demographics	X														
Medical History	X														
Clinical laboratory assessments[b]	X			X		X		X						X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X														X
Electrocardiogram	X														
Physical Examination	X	X						X						X	
Muscle function tests[e]	X	X						X						X	
Pulmonary function tests[f]	X	X						X						X	
Cardiac MRI	X														
Forearm muscle MRI	X														
Specialty labs[g]		X	X												X
FG-3019 infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire		X													X

Abbreviations: MRI, magnetic resonance imagery; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected prior to start, within 15 minutes of infusion completion, and within 15 minutes of completing the observation period
d. Weight to be collected in screening and every 6 months thereafter. Height (measured from ulna length and arm span) to be collected at screening and end of treatment.
e. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test
f. Pulmonary function tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
g. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details

Appendix 2 Schedule of Assessments: First Year of Treatment (Weeks 28 through 52)

Assessment[a]	Treatment Period (Weeks)												
	28	30	32	34	36	38	40	42	44	46	48	50	52
Clinical laboratory assessments[b]					X						X		
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]													X
Electrocardiogram													X
Physical Examination					X						X		
Muscle function tests[e]					X						X		
Pulmonary function tests[f]					X						X		
Cardiac MRI													X
Muscle MRI (forearm)													X
Specialty labs[g]													X
FG-3019 infusion	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire													X

Abbreviations: MRI, magnetic resonance imagery; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected prior to start, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight to be collected in screening and every 6 months thereafter. Height (measured from ulna length and arm span) to be collected at screening and end of treatment.
e. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test
f. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
g. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details

Appendix 3 Schedule of Assessments: Second Year of Treatment and Post-Treatment Assessments

	Treatment Period (Weeks)										Post-Treatment
Assessment[a]	**54, 56, 58**	**60**	**62, 64, 66, 68, 70**	**72**	**74, 76, 78, 80, 82**	**84**	**86, 88, 90, 92, 94**	**96**	**98, 100, 102**	**104/ EOT**	**Week 112 ±7 days or 10 Weeks After Last Dose for Early Termination**
Clinical laboratory assessments[b]		X		X		X		X			X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]					X					X	
Electrocardiogram										X	
Physical Examination		X		X		X		X		X	X
Muscle function tests[e]		X		X		X		X		X	
Pulmonary function tests[f]		X		X		X		X		X	
Cardiac MRI										X	
Muscle MRI										X	
Specialty labs[g]					X				X	X	
FG-3019 infusion	X	X	X	X	X	X	X	X	X		
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire										X	

Abbreviations: EOT= end of treatment; MRI, magnetic resonance imagery, PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected prior to start, within 15 minutes of infusion completion and within 15 minutes of completing the observation period
d. Weight to be collected in screening and every 6 months thereafter. Height (measured from ulna length and arm span) to be collected at screening and end of treatment.
e. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test
f. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
g. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details

Appendix 4 Pharmacokinetic and Pharmacodynamic Sampling Times

		Treatment Period										Post-Treatment
Sample	**Timepoint**	**Day 0**	**Day 2 ±1 day**	**Day 4 ±1 day**	**Day 7 ±1 day**	**Day 10 ±1 day**	**Week 2**	**Week 26**	**Week 52**	**Week 78**	**Week 102**	**Week 112 ±7 days or 10 Weeks After Last Dose for Early Termination**
FG-3019 PK[a]	Before infusion	X					X	X	X	X	X	
	Within 1 hour after infusion	X							X		X	
	Time point sample (no infusion)		X	X	X	X						
HAHA[b]	Predose (when applicable)	X										X
CTGF[c]	Predose (when applicable)	X										X
Exploratory[d]	Predose (when applicable)	X							X		X	X

Abbreviations: CTGF = connective tissue growth factor; HAHA = human anti-human antibody; PK = pharmacokinetic

a. Approximately 1-2 mL of blood will be collected for each measurement of FG-3019 PK.
b. Approximately 1 mL of blood will be collected for each measurement of HAHA.
c. Blood and urine samples will be collected. Approximately 1 mL of blood and 0.5 mL of urine will be collected for each measurement of CTGF.
d. Approximately 5 mL of blood will be collected for each exploratory sample.

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
PROTOCOL NUMBER:	FGCL-3019-079
PHASE:	2
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	126630
STUDY DRUG:	FG-3019
INDICATION:	Duchenne Muscular Dystrophy
FIBROGEN MEDICAL MONITOR	Name: [redacted] FibroGen, Inc. Title: [redacted] Telephone: [redacted] Mobile/Pager: [redacted] E-mail Address: [redacted]
ORIGINAL PROTOCOL:	16 June 2015
AMENDMENT 1.0	31 August 2015

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy

FGCL-3019-079

Original: 16 June 2015

Amendment 1.0: 31 August 2015

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen at the address provided below. Please retain the original for your study files.

[redacted]
FibroGen, Inc.
409 Illinois Street
San Francisco, California 94158 USA

FG-3019 Protocol FGCL-3019-079 Amendment 1.0

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 16 June 2015

Amendment 1.0: 31 August 2015

This protocol is approved by FibroGen.

[redacted] 8/31/2015

[redacted] FibroGen Inc. Date

AMENDMENT 1.0: KEY CHANGES FROM ORIGINAL PROTOCOL

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Key Change	Rationale	Sections Affected
Delete exploratory endpoint: Effect of concomitant corticosteroid treatment on LVEF and cardiac fibrosis	Entry criteria now only allow recruitment of subjects on corticosteroids	Synopsis 4.1.3 Exploratory Endpoints
Inclusion criterion #3: Specified wheelchair dependent for <5 years	Decrease heterogeneity in subject population	Synopsis 5.1 Inclusion Criteria
Inclusion criterion #11: Increased length of stable regimen of heart failure cardiac medications prior to screening from 6 weeks to 3 months	Decrease probability of recruiting subjects with unstable cardiac condition at baseline	Synopsis 5.1 Inclusion Criteria
Exclusion criterion #4: Severe uncontrolled heart disease including any of the following: Need for intravenous diuretics or inotropic support increased from within 6 weeks to at least 3 months prior to screening; Hospitalization for a heart failure exacerbation or arrhythmia increased from last 6 weeks to last 3 months	Align with modified inclusion criterion #11	Synopsis 5.1 Inclusion Criteria
Inclusion criterion #12: Deleted option of no corticosteroid use for at least 6 months prior to screening and throughout the study participation	Increase homogeneity of patient population	Synopsis 5.1 Inclusion Criteria
Stable treatment with corticosteroids at baseline now mandated and no longer an option	Increased homogeneity of patient population	9.3.3 Demographics and Baseline Characteristics
Changed duration of follow-up period from 6 weeks to 10 weeks	The length of the AE reporting period was increased to align the AE reporting period (previously 6 weeks after the last dose) to the study follow-up period (10 weeks).	4.2 Trial Overview 7.1.4 Early Withdrawal 7.1.5 Follow-up Period 8.3.1 Adverse Event Reporting Period 8.3.2 Adverse Event Eliciting/Reporting 8.3.5.2 Deaths
Use of deflazacort, if regarded by the principal investigator as standard of care, is allowed.	Although an investigational drug in the USA, it is regarded as standard of care for this patient population by participating investigative sites.	Synopsis 4.4 Concomitant Medications, Procedures and Nondrug Therapies 5.2 Exclusion Criteria

PROTOCOL SYNOPSIS

Study Title:	Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
Protocol Number:	FGCL-3019-079, Amendment 1.0
Investigational Product:	FG-3019 (Recombinant fully human IgG_1 kappa monoclonal antibody to connective tissue growth factor)
Study Phase:	Phase 2
Target Population:	Non-ambulatory subjects with Duchenne muscular dystrophy (DMD)
Number of Subjects Planned:	22
Study Centers Planned:	Up to 10 centers

OBJECTIVES

Primary Objective

To estimate FG-3019's efficacy in non-ambulatory subjects with DMD

Secondary Objectives

1. To evaluate safety and tolerability of FG-3019 administered intravenously every 2 weeks
2. To assess pharmacokinetics of FG-3019 in the targeted pediatric population
3. To evaluate pharmacodynamic markers of FG-3019's effects in DMD

ENDPOINTS/ASSESSMENTS

Efficacy

Primary Endpoint

- Difference in annual forced vital capacity (FVC) (% predicted) decline during treatment of FG-3019 compared with the estimated annual decline prior to FG-3019 treatment.

Secondary Endpoints

- Change from baseline to 1 year in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow

- Change in LVEF from baseline to 1 year
- Change from baseline to 1 year in Performance of Upper Limb (PUL) Score
- Change from baseline to 1 year in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to 1 year in cardiac fibrosis score assessed by magnetic resonance imaging (MRI)
- Change from baseline to 1 year in forearm muscle fat and fibrosis assessed by MRI
- Changes from baseline to 2 years in the efficacy parameters

Exploratory, Pharmacokinetics, Pharmacodynamics

- Pharmacokinetic (PK) profile of FG-3019 (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$)
  - In the overall population
  - In subjects 12 to 16 years of age, inclusive
  - In subjects older than 16 years
  - Comparison of PK profiles across age groups
- Plasma and urine connective tissue growth factor (CTGF)
- Creatine kinase (CK)
- Circulating biomarkers

Safety

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

STUDY DESIGN

This study will be an open-label, single arm study of up to 22 subjects. Each subject will receive FG-3019 (35 mg/kg, every 2 weeks) for 2 years. All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow). An interim analysis of safety and efficacy will be performed after all evaluable subjects complete one year of dosing.

If this analysis indicates a potential benefit, the study will be continued through Week 112 to determine the further course of any trends in efficacy and safety parameters observed after 52 weeks of treatment.

STUDY PROCEDURES

Details regarding study procedures are provided as follows:

Appendix 1: Screening Period through Week 26

Appendix 2: Week 28 through Week 52

Appendix 3: Year 2 and Post-Treatment

Appendix 4: Pharmacokinetic and Pharmacodynamic Sampling Times

MAIN SELECTION CRITERIA

Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory; wheelchair dependent for <5 years
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (forearm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. Estimated annual decline of FVC (% predicted) of ≥5% based upon at least 2 PFTs done in the previous 18 months, in addition to the screening FVC.
10. Left ventricular ejection fraction >45%
11. Stable regimen of heart failure cardiac medications (e,g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation.
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >10 g/dL
    c. Absolute neutrophil count >1000/mcL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤2x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after last dose of study drug.

Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation

2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 2 years of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 1 year
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI $\geq$40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug within 28 days prior to start of study treatment
11. Ongoing participation in any other therapeutic clinical trial. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

TREATMENTS

FG-3019 Dose, and Mode of Administration

Each subject will receive FG-3019 (35 mg/kg, every 2 weeks) for 2 years. The dose of FG-3019 (35 mg/kg) for each infusion should be based on body weight obtained during screening. If a subject has a weight change of more than 10%, the total FG-3019 dose will be adjusted based on the new weight.

Reference Therapy: Not applicable

Concomitant Medications/Therapies: Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy. Investigational agents and currently investigational agents that receive marketing authorization during this trial are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed. Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

STATISTIC METHODS

This study will enroll up to 22 subjects. A sample size of 22 subjects will provide 84% power to detect an absolute difference of 3.5% in FVC % predicted, using a two-sided, one-sample paired t-test to compare the annual change posttreatment with that prior to treatment at significance level 0.05. This calculation is based on assumption of standard deviation of 5% and assumption of two dropouts without any efficacy

assessments at study completion.

The primary basis for assessment of efficacy will be the capacity of FG-3019 to reduce the rate of deterioration of FVC. The primary endpoint is the difference in annual FVC (% predicted) decline during treatment with FG-3019 compared with the annual decline prior to treatment with FG-3019. The posttreatment annual change in FVC (% predicted) will be compared to that prior to treatment using a mixed effect repeated measures model (MMRM), with adjustment of baseline FVC % predicted and use of corticosteroid. Effect of age (≤16 versus >16) and effect of disease characteristics at baseline, such as time since loss of ambulation, use of ventilation, spine surgery, type of genetic mutation, will be evaluated and may be included in analysis models as appropriate. The difference in annual decline rate will be presented in two-sided 95% confidence interval. Two-sided test on whether the difference is significantly different from zero will be reported.

The analysis of the primary endpoint will be based on the Full Analysis Set population. For subjects who drop out of the study early, their annual change in FVC % predicted will be estimated via the combination of available assessments and the MMRM model.

Change from baseline to one year and to two years in FVC (% predicted) will be estimated via the above mentioned MMRM model. If a substantial number of subjects drop out of the study before entering Year 2 treatment, change from baseline to 2 years will be estimated only for the subset of subjects who have provided Year 2 efficacy assessment.

Summary statistics for observed values, change from baseline, and percent change from baseline will be reported for all secondary endpoints. For those secondary outcomes where historical data is available, the effect of FG-3019 may be investigated further by performing repeated measures analyses.

FG-3019 concentrations and derived PK parameters will be tabulated and summarized using descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters. Attainment of steady-state will be investigated.

Safety analyses will include summary of adverse events (including treatment emergent AEs, treatment emergent serious AEs, deaths, and infusion-associated AEs), prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs), and physical exams.

TABLE OF CONTENTS

LIST OF APPENDICES

2 BACKGROUND

2.1 Description of FG-3019

FG-3019 is a recombinant fully human immunoglobulin G_1 (IgG) kappa monoclonal antibody to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role. These diseases include liver fibrosis due to hepatitis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne muscular dystrophy (DMD). FG-3019 (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. FG-3019 contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2 Duchenne Muscle Dystrophy

Duchenne muscular dystrophy (DMD) is usually inherited in an X-linked recessive fashion, but it can occur as a result of spontaneous mutation in boys from families without a known history of the condition. On the basis of some 40 studies including several million male births, incidence at birth of Duchenne muscular dystrophy is around 1:3300, and its prevalence in the population (in terms of the total male population) is around 1:16500 (Emery, 1991).

DMD is a result of mutations (mainly deletions) in the dystrophin gene (DMD; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration with loss of independent ambulation by the age of 13 years (Bushby, 2010).

In skeletal muscles of DMD patients constant myofiber breakdown results in persistent activation of myofibroblasts and altered production of extracellular matrix (ECM) resulting in extensive fibrosis. Muscle fibrosis is the only myo-pathologic parameter that significantly correlated with poor motor outcome as assessed by quadriceps muscle strength, manual muscle testing of upper and lower limbs, and age at ambulation loss (Desguerre, 2009).

Patients with DMD are generally wheelchair bound before they develop significant respiratory muscle weakness. Respiratory complications are the primary cause of morbidity and mortality in DMD as progressive respiratory muscle weakness leads to hypoventilation and/or recurrent atelectasis and pneumonia, secondary to decreased cough effectiveness (McKim, 2012).

After age 10 to 14, patients gradually begin to lose respiratory muscle function based on pulmonary function tests (PFTs) such as forced vital capacity (FVC). The median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001, Tangsrud, 2001).

Because of improvements in respiratory care, cardiac dysfunction is now a leading cause of morbidity and mortality in DMD patients (Schram, 2013). Progressive myocardial fibrosis, as detected by late gadolinium enhancement (LGE), is strongly correlated with the left ventricular ejection fraction (LVEF) decline in Duchenne muscular dystrophy patients. Longer steroid treatment duration is associated with a lower age-related increase in myocardial fibrosis burden (Tandon, 2015).

2.2.1 Relevance of Connective Tissue Growth Factor (CTGF) in DMD

Connective tissue growth factor (CTGF) is a nonstructural regulatory protein present in the extracellular matrix that has an important role in fibrosis. Skeletal muscle from DMD patients, dystrophic dogs, and mdx mice all show elevated levels of CTGF (Sun, 2008).

CTGF can reproduce or amplify the effects of TGFβ on fibrosis by inducing collagen type 1, α5 integrin, and fibronectin much more potently than TGFβ in fibroblasts (Kharraz, 2014).

Comparison of mdx mice with normal or genetically depleted levels of CTGF revealed that exercised mice with reduced CTGF developed less fibrosis and exhibited better muscle strength than mice with normal levels of CTGF (Morales, 2013). In culture, both myoblasts and myotubes were shown to express and secrete CTGF to the medium, and respond to the growth factor by increasing the extracellular matrix constituents, partially inhibiting myoblasts differentiation and inducing myoblasts dedifferentiation (Vial, 2008).

In DMD, the role of CTGF might extend well beyond replacement fibrosis secondary to loss of muscle fibers, since its overexpression in skeletal muscle could by itself induce a dystrophic phenotype (Morales, 2013).

A major feature of the hearts of DMD patients is cardiac fibrosis. Cardiac fibrosis is associated with increased CTGF expression in the *mdx* mouse heart. CTGF may be a key mediator of early and persistent fibrosis in dystrophic cardiomyopathy (Au, 2011).

CTGF is critically involved in several chronic fibro-degenerative diseases. FG-3019 treatment has been shown to positively the affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.

2.3 A Summary of Relevant Findings from Nonclinical Studies and from Clinical Trials

Please refer to the most recent version of FG-3019 Investigator's Brochure.

2.3.1 Nonclinical Studies

In DMD, the genetic loss of the cytoskeletal protein dystrophin results in muscle damage that, leads to progressive replacement of muscle with fibrotic and fat tissue. This progressive muscle damage can be recapitulated in the DMD mouse model (*mdx*), and accelerated by muscle usage (Pessina, 2014).

As was observed with genetic depletion of CTGF, pharmacologic inhibition of active CTGF in *mdx* mice by treatment with FG-3019 resulted in reduced fibrosis and skeletal muscle damage, as well as improved preservation of skeletal muscle strength in isolated muscles. The FG-3019 treated *mdx* mice were also subjected to a test of exercise endurance, in which they showed better performance than *mdx* mice injected with control IgG (Morales, 2013).

FG-3019 treatment of *mdx* mice was associated with decreased skeletal muscle damage and fibrosis, decreased collagen III and fibronectin expression, decreased plasma creatinine kinase (CK) (Morales, 2013), and increased isometric force of skeletal muscle (Morales, 2011).

2.3.2 Pharmacokinetics

Key findings are summarized below from Phase 1 and 2 studies investigating the pharmacokinetics (PK) of FG-3019 in subjects with diabetic kidney disease, idiopathic pulmonary fibrosis, and pancreatic cancer:

- FG-3019 was administered over the dose range of 3 to 45 mg/kg every 2 weeks and 17.5 to 22.5 mg/kg weekly.
- FG-3019 exposure (e.g., mean/median C_{max} and C_{min}, area under the curve [AUC]) generally increased with increasing dose.
- The $t_{1/2}$ was approximately 1 to 2 weeks at doses >25 mg/kg in a trial in pancreatic cancer subjects.

2.3.3 Safety

Key findings are summarized below from the Phase 1 and 2 studies involving more than 400 adults with diabetic kidney disease, idiopathic pulmonary fibrosis, and liver fibrosis due to hepatitis B or pancreatic cancer:

- Overall, FG-3019 was well tolerated across the range of doses noted above, and there were no dose-limiting toxicities.
- Treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity and transient in duration.
- Infusion-related reactions have been mild-to-moderate and did not recur following re-administration of FG-3019
- TEAEs were considered typical of the subjects' underlying medical condition(s) and, in the placebo-controlled studies, were equally distributed between placebo and FG-3019 treatment groups.
- No apparent pattern to TEAEs that occurred within 24 hours after infusions was observed.
- No apparent pattern for treatment-emergent serious adverse events (TESAEs) was observed during clinical testing.

2.3.4 Efficacy

Key efficacy findings are summarized below from the Phase 1 and 2 studies of CTGF inhibition by FG-3019 in indications other than DMD.

2.3.4.1 Pancreatic Cancer

Biweekly doses of up to and including 45 mg/kg and weekly doses of 17.5 and 22.5 mg/kg were administered to subjects with previously untreated locally advanced or metastatic pancreatic adenocarcinoma. Increased exposure to FG-3019 was associated with increased survival. There appears to be a relationship between survival and trough blood levels of FG-3019 (C_{min}). Notably C_{min} >150 mcg/mL after the first dose of FG-3019 (Day 15) was associated with significantly increased progression free survival and overall survival.

A maximal effect in survival benefit was achieved at dose levels of 25 to 45 mg/kg/2 weeks.

2.3.4.2 Idiopathic Pulmonary Fibrosis (IPF)

In subjects with IPF who completed 45 weeks of dosing with 15 or 30 mg/kg FG-3019, approximately 40% of subjects had stable or improved lung fibrosis by quantitative high resolution CT imaging compared to baseline values with approximately 30% having improved pulmonary fibrosis.

Overall, subjects with stable or improved lung fibrosis also had stable or improved FVC (% predicted).

2.4 Risks and Benefits

FG-3019 has been generally well tolerated with most adverse events being typical of those expected for subjects with the underlying disease conditions.

Infusion-related reactions have been rarely observed in some subjects treated with FG-3019. Across studies in other indications, infusion-related reactions have been mild-to-moderate did not result in discontinuation of treatment with FG-3019, and did not result in the use of prophylaxis for subsequent infusions.

The favorable experience with FG-3019 to date does not exclude the possibility of more severe infusion reactions occurring in future subjects.

This is the first clinical study of FG-3019 in DMD. There are currently no confirmed benefits to subjects with DMD treated with FG-3019. However, a potential benefit of treatment with FG-3019 is indicated in preclinical models of DMD and previous clinical studies of FG-3019 in other indications where CTGF is also associated with disease progression.

Dose regimen equal to or exceeding 35 mg/kg have been implemented in other indications in adult subjects. The objective of these studies was to inhibit bioactive CTGF, which is associated with disease progression in a number of indications. Please refer to the Investigator's Brochure for a comprehensive summary of efficacy, safety, and exposure data.

The current study will explore the clinical relevance of CTGF inhibition, as indicated in preclinical models, in DMD patients.

2.5 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Periods

FG-3019 is administered as an IV infusion at a dose of 35 mg/kg every two weeks for two years (Week 0 to Week 102). The dose, frequency and route of administration correspond with dose regimens that were well tolerated and possibly associated with efficacy in clinical studies in adults with IPF and pancreatic cancer. In both of these indications FG-3019 was administered at doses that included the targeted dose regimen for the current study (35 mg/kg bodyweight) and greater (45 mg/kg bodyweight). These doses were not associated with dose limiting toxicity.

The overall objective of all of these studies, including the current study, is to provide a dose associated with clinically relevant CTGF blockade to impede progression of serious disease states. Body weight-related dosing and utilization of a dose no greater than the maximal dose used in adults are expected to ensure that systemic exposure in the targeted pediatric population will not exceed the systemic exposure achieved in adults.

PK assessments will be done during the course of the study and facilitate ongoing monitoring of exposure to FG-3019 during the course of the study.

The planned treatment duration is no longer than total treatment periods achieved in previous studies with FG-3019.

The duration of treatment of the current study is also similar to the duration of other studies in DMD and is expected to provide sufficient basis to evaluate potential benefit in the targeted pediatric population with DMD.

2.6 Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents. Detailed information regarding study conduct is found in Sections 10, 11, 12, and 13.

2.7 Population to be Studied

Non-ambulatory adolescents and adults with DMD will be enrolled in this trial.
A detailed inclusion/exclusion list is provided in Section 5.

3 OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is to estimate FG-3019's efficacy in non-ambulatory subjects with DMD.

3.2 Secondary Objectives

The following are the secondary objectives of this trial:

1. To evaluate safety and tolerability of FG-3019 administered intravenously every 2 weeks
2. To assess pharmacokinetics of FG-3019 in the targeted pediatric population
3. To evaluate pharmacodynamic markers of FG-3019's effects in DMD

4 STUDY DESIGN

4.1 Endpoints and Assessments

4.1.1 Primary Endpoint

The primary endpoint is the difference in annual forced vital capacity (FVC) (% predicted) decline during treatment of FG-3019 compared with the estimated annual decline prior to FG-3019 treatment.

4.1.2 Secondary Endpoints

The following are the secondary endpoints:

- Change from baseline to 1 year in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow
- Change in LVEF from baseline to 1 year
- Change from baseline to 1 year in Performance of Upper Limb (PUL) Score
- Change from baseline to 1 year in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to 1 year in cardiac fibrosis score assessed by MRI
- Change from baseline to 1 year in forearm muscle fat and fibrosis assessed by MRI
- Changes from baseline to 2 years in the efficacy parameters

4.1.3 Exploratory, Pharmacokinetic and Pharmacodynamic Outcome Measures

Exploratory outcome measures for this trial are:

- Pharmacokinetic (PK) profile of FG-3019 (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$)
    - In the overall population
    - In subjects 12 to 16 years of age, inclusive
    - In subjects older than 16 years
    - Comparison of PK profiles across age groups
- Plasma and urine CTGF
- Creatine kinase (CK)
- Circulating biomarkers

4.1.4 Safety Assessments

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

4.2 Trial Overview

This study will be an open-label, single arm study of up to 22 subjects. Each subject will receive FG-3019 (35 mg/kg, every 2 weeks) for up to 2 years. All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow) on a continuous basis.

An interim analysis of safety and efficacy will be performed after all evaluable subjects complete one year of dosing. If this analysis indicates a potential positive benefit/risk, the treatment will continue through Week 102 to determine the further course of any trends in efficacy parameters observed after 52 weeks of treatment. Upon completion of treatment or premature discontinuation from the trial, subjects will be asked to return to the investigative site to complete final safety and efficacy assessments 10 weeks after the last dose of FG-3019.

4.3 Study Treatment

4.3.1 Dose and Schedule

Each subject will receive FG-3019 (35 mg/kg) intravenously every 2 weeks (q2w). See Section 6 for detailed information on study drug formulation, storage, and administration.

4.3.2 Rationale for Dose and Schedule

The FG-3019 dose is based on results of a study in adult subjects with pancreatic cancer. In that study (Section 2.3.4.1), minimum FG-3019 blood levels (C_{min}) ≥150 mcg/mL were associated with increased median survival and 1 year survival compared to subjects with C_{min} <150 mcg/mL. Given the apparent threshold effect for increased benefit when minimal FG-3019 exposure is ≥150 mcg/mL and based on PK analysis using these data, the planned dose of 35 mg/kg administered every 2 weeks is projected to achieve this minimum exposure in the targeted DMD study population.

4.4 Concomitant Medications, Procedures and Nondrug Therapies

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy.

Investigational agents and currently investigational agents that receive marketing authorization during this trial are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

Concomitant medications (any prescription and/or over-the-counter [OTC] preparation) and procedures or nondrug therapies (e.g., physical therapy or acupuncture) used by a subject while participating in this clinical trial must be recorded from the Screening Visit through the End-of-Study Visit.

Questions regarding potential impact of concomitant medications on evaluability of subjects enrolled in the study should be addressed to the attention of the FibroGen Medical Monitor or designee.

4.4.1 Contraception

Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy of a partner must be reported (Section 8.3.6).

4.5 Safety Plan

An ongoing safety review is facilitated by the unblinded nature of the study. FibroGen will review safety data and will communicate the results of these reviews to investigators by email or teleconference on a regular basis. In addition, FibroGen will review safety experience with investigators during teleconferences that will be held at least quarterly and include the conclusions of the Data Monitoring Committee's (DMC) latest data review.

FibroGen will notify investigators immediately if a new safety risk is identified.

4.6 Data Monitoring Committee

A DMC will be utilized and will be composed of external and internal (FibroGen) experts. Composition and responsibilities of the DMC are defined in a separate DMC charter.

DMC responsibilities include review of safety data, available pharmacokinetic data, and pulmonary function tests.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory; wheelchair dependent for <5 years
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (forearm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. Estimated annual decline of FVC (% predicted) of ≥5% based upon at least 2 PFTs done in the previous 18 months, in addition to the screening FVC
10. Left ventricular ejection fraction >45%
11. Stable regimen of heart failure cardiac medications (e,g, angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >10 g/dL
    c. Absolute neutrophil count >1000/mcL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤2x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after the last dose of study drug

5.2 Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 2 years of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 1 year
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug within 28 days prior to start of study treatment
11. Ongoing participation in any other therapeutic clinical trial. Use of deflazacort if regarded by the principal investigator as standard of care is allowed

5.3 Subject Withdrawal

Subjects may withdraw from the study at any time.

The investigator will remove a subject from study treatment for the following reasons:

- Adverse events, which in the opinion of the Principal Investigator and/or FibroGen preclude further study drug dosing
- Nonadherence to protocol-defined procedures, in particular missing of 3 or more sequential study drug infusions
- Not available for safety assessments

Subjects who discontinue the study early should be strongly encouraged to complete the evaluations described in Section 7.1.3.

5.4 Replacement of Subjects

Subjects may be replaced in this study if a subject’s participation is not terminated due to safety or tolerability issues and is replaced prior to completion of targeted recruitment of 22 subjects into the study. Replacement decisions will be made between the sponsor and investigator on a case-by-case basis.

5.5 Study Termination

This trial can be terminated by the sponsor at any time for any reason.

6 STUDY DRUG/TREATMENT SUPPLY

6.1 FibroGen Investigational Product

FG-3019 is a fully human IgG_1 kappa monoclonal antibody that binds to CTGF.

6.1.1 Formulation

FG-3019 is supplied in single-use glass vials containing 10 mL of a sterile, preservative-free solution. The solution is composed of 10 mg/mL FG-3019, 1.60 mg/mL l-histidine, 3.08 mg/mL l-histidine HCl, 8.01 mg/mL sodium chloride and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0.

6.1.2 Storage

Vials of FG-3019 must be stored refrigerated (2°C to 8°C), temperature-controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation.

6.1.3 Preparation of Dose for Administration

The dose of FG-3019 (35 mg/kg) for each infusion should be based on body weight obtained during screening. If a subject has a weight change of more than 10%, the total FG-3019 dose will be adjusted based on the new weight. FG-3109 may be administered undiluted or, for convenience of infusion, may be diluted with 0.9% Sodium Chloride Injection according to the Dose Preparation Instructions in the Study Reference Investigational Product (IP) Manual.

FG-3019 will be administered as soon as possible after release from the site's pharmacy and within 24 hours of preparation. FG-3019 will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

6.1.4 Administration

Agent	Dose	Route	Schedule
FG-3019	35 mg/kg	IV, over 1 hour	q 2 weeks
DO NOT ADMINISTER FG-3019 AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.			

Subjects should be carefully monitored for reaction during the first infusion with a physician available as needed. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation for the initial 3 infusions. The IV access should remain in place and maintained per site procedures until the end of this posttreatment observation period. If a subject does not have an infusion reaction (Section 8.2.3) during 3 consecutive infusions, the infusion duration may be shortened to as little as 30 minutes provided the Investigator thinks infusing this fluid load is safe. The post-infusion observation period will remain as 1 hour.

If a subject has an infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences an infusion reaction and continues FG-3019 dosing, a physician must be immediately available during subsequent infusions and observation periods until the subject does not have any infusion reaction for three sequential infusions.

Premedication, such as antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are not normally administered before infusions of FG-3019. Premedication may be used for subjects who experience infusion reactions at the discretion of the investigator after discussion with the Medical Monitor.

FG-3019 will be administered in a hospital or ambulatory setting with adequate facilities for managing medical emergencies for at least three infusions to confirm the subject does not have an infusion reaction. The study site must have trained staff and medications for the treatment of acute reactions, including anaphylaxis, immediately available. There is no specific treatment for an FG-3019 overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

7 ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

7.1 Study Procedures by Visit

All study procedures and assessments will be performed in accordance with the Schedule of Assessments presented in Appendix 1 (Screening Period through Week 26), Appendix 2 (Weeks 28 through 52), Appendix 3 (Second Year of Treatment and Post-Treatment Assessments), and Appendix 4 (Pharmacokinetic and Pharmacodynamic Sampling Times).

For all potential subjects, screening procedures required to determine subject eligibility will be performed within 28 days prior to Day 0 (first infusion of FG-3019). Potential subjects may be re-screened if initial screening procedures lie outside the 28-day screening period prior to planned study entry.

Subject's eligibility for this study will be reviewed and approved by Sponsor's medical monitor prior to subject enrollment.

The following assessments are relevant to the assessment of efficacy: pulmonary function tests (FVC, mean inspiratory flow (MIF), peak expiratory flow), Brooke Upper Extremity Rating Scale, Performance of the Upper Limb, pinch strength, grip strength, cardiac MRI, and muscle MRI. Refer to the Study Reference Manual for details.

Approved windows for performing study assessments are defined in the following sections.

7.1.1 Screening Period (no earlier than Day -28)

Assessments to be conducted during the screening period are presented in Appendix 1.

Screening assessments may be completed over several visits during the screening period. It is recommended that the less invasive screening assessments be performed first upon completion of the signed Informed Consent and/or Assent Form [ICF] (demographics, medical history, blood draws, electrocardiogram [ECG], vital signs (includes body weight and height), physical exam, pulmonary function tests (PFTs), and then followed by the more rigorous screening assessments (i.e., muscle function tests, cardiac MRI).

A cardiac MRI performed within 3 months prior to Day 0 (start of dosing) is acceptable to confirm eligibility based on the LVEF study entry criterion and as baseline cardiac MRI. If this historic MRI is not available, a cardiac MRI must be performed during the Screening Period.

A forearm muscle MRI may be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Muscle and pulmonary function tests (PFTs) will be performed during the screening period. Muscle function and PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.

In addition, an exploratory blood sample will be drawn for analysis of circulating biomarkers of fibrosis and specific muscle miRNAs (dystromirs) prior to first FG-3019 infusion.

7.1.2 Dosing Period

The dosing period begins on the first day of dosing with study treatment (Week 0) and continues through Week 102. Subjects will receive study drug every 2 weeks.

The visit window for all dosing visits is ±2 days.

Assessments and procedures to be performed during the dosing period are presented in Appendix 1 (Screening Period through Week 26), Appendix 2 (Weeks 28 through 52), and Appendix 3 (Second Year of Treatment and Post-Treatment).

Muscle or pulmonary function tests that cannot be performed or produce inadequate results according to test procedures during a specified visit should be performed by the next scheduled dosing visit.

Both cardiac and muscle MRIs may be performed within ±2 weeks of the specific visit.

Blood samples will be drawn for pharmacokinetic analysis according to the schedule in Appendix 4. Blood draws to be collected on non-dosing days may be collected within ±1 day as outlined in Appendix 4.

7.1.3 End of Treatment (Per-Protocol)

Assessments and procedures to be conducted after the last dose of study drug are presented in Appendix 3.

The end of treatment cardiac and muscle MRIs may be performed any time from Week 104 and Week 112.

7.1.4 Early Withdrawal from Treatment

Subjects who prematurely discontinue the study should be strongly encouraged to complete the safety and efficacy evaluations scheduled for Week 104. All subjects should be encouraged to undergo follow-up 10 weeks (±7 days) after the last dose of FG-3019 for evaluation of adverse events.

7.1.5 Follow-Up Period

The follow-up period begins after subjects have Year 2 efficacy evaluations done at Week 104, or at premature study termination. The assessments should be completed 10 weeks (±7 days) after the last dose of FG-3019.

7.1.6 Missed Visits

Every attempt must be made to complete all study visits as outlined in the Schedules of Assessments. Missed infusions will not be replaced. If a subject misses a scheduled efficacy assessment, the assessment should be performed as soon after the missed visit as feasible.

7.1.7 Unscheduled Visits

Unscheduled Visit assessments may be required at the discretion of the investigator.

7.2 Assessments

Please refer to the Schedules of Assessments (Appendix 1, Appendix 2, Appendix 3, and Appendix 4) for the scope and timing of assessments. Please refer to the Laboratory Manual for details regarding laboratory sample collection and processing; and the Study Reference Manual for details regarding the conduct of functional tests and MRIs.

7.2.1 Pulmonary Function Tests

The following pulmonary function tests (PFTs) will be performed to assess changes in lung function: forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow rate (PEF; PEFR), forced expiratory volume in 1 second (FEV1), and peak cough flow (Mayer, 2015, Miller, 2005).

7.2.2 Muscle Strength and Functional Measurements

The following assessments will be performed to assess changes in upper extremity strength and function: Brooke Upper Extremity Rating Scale (Brooke Scale), Performance of the Upper Limb (PUL), Grip Test, and Pinch Strength Test.

7.2.3 Cardiac MRI

Cardiac MRIs, will be performed at baseline (Day 0) and at yearly intervals to assess changes in left ventricular ejection fraction (LVEF) and presence of late gadolinium enhancement (LGE), a marker for myocardial fibrosis.

7.2.4 Forearm Muscle MRI

Forearm muscle MRIs will be performed at baseline (Day 0) and at yearly intervals to assess changes in degree of fatty replacement of select muscle groups by T2 relaxation time mapping.

7.2.5 Quality of Life Questionnaire

Pediatrics Outcomes Data Collection Instrument (PODCI) Quality Outcome Questionnaire will be performed to assess if treatment with FG-3019 improves quality of life.

7.2.6 Vital Signs and Physical Examinations

A physical examination will be performed at screening and baseline (Day 0), every 12 weeks and at end of treatment and post-treatment follow-up. Examinations in screening, Week 52 (±2 weeks) and Week 104 (±2 weeks) should be complete examinations. Other examinations may be disease-specific or problem-oriented examinations.

Vital signs (pulse, respiration, sitting blood pressure, and temperature) will be collected at screening and prior to start of each infusion, within 15 minutes of the end of each infusion, and within 15 minutes of the completion of the post-infusion observation period.

7.2.7 Laboratory Assessments

All laboratory tests of blood and/or urine specimens will be performed at a central laboratory or FibroGen, as appropriate. A Central Laboratory Manual with instructions

on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local clinical laboratories will be used to assess and facilitate the management of adverse events and to provide usual standard of care. Local clinical laboratory data will not be collected in the study database except for abnormalities that are reported as adverse events.

7.2.7.1 Safety Assessments

Blood samples will be 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.

7.2.7.2 Pharmacokinetics

Plasma concentrations of FG-3019 will be determined on Day 0 pre-dose and within 1 hour post infusion, then on Days 2, 4, 7, 10, and 14. The Day 14 sample should be on the same day of, but prior to the start of the next infusion of study drug.

Day 2, 4, 7, and 10 PK assessments represent target days following the first dose; however, actual sample collection time of up to ±1 day of the target time is acceptable as long as the actual time of dosing and actual time of each sample collection are recorded accurately.

At Weeks 26, 52, 78, and 102, trough FG-3019 levels (C_{min}) will be determined prior to study drug infusion.

PK samples will also be drawn within 60 minutes of infusion completion on Weeks 52 and 102.

7.2.7.3 Plasma and Urine CTGF

Plasma and urine samples will be analyzed for CTGF concentrations from samples taken as described in Appendix 4.

7.2.7.4 HAHA

Blood samples will be drawn for analysis of human anti-human antibody (HAHA) according to the schedule in Appendix 4.

7.2.7.5 Biomarkers

Blood samples will be drawn for analysis of biomarkers. The exact biomarkers will be based on current scientific knowledge regarding CTGF, FG-3019 and DMD at the time the tests are performed. No genetic testing will be performed.

8 ASSESSMENT OF SAFETY

8.1 Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 1 (Screening Period through Week 26), Appendix 2 (Weeks 28 through 52), and Appendix 3 (Second Year of Treatment and Post-Treatment). In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the Study Drug.

8.2 Definitions

8.2.1 Definition of an Adverse Event (AE)

For the purpose of this study, an AE is any untoward medical occurrence that occurred in the protocol-specified AE reporting period, and which does not necessarily have a causal relationship with the study drug. An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.3.1).

8.2.2 Definition of a Serious Adverse Event (SAE)

A **serious adverse event** is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.2.3 Definition of an Infusion Reaction

Infusion reactions are immunologic reactions to an infused protein, and are different from events resulting from the process of infusing the protein (e.g., infusion site bruise) and are different from adverse events due to the infused protein's intended or unintended pharmacologic effects.

8.2.3.1 Acute Infusion Reaction

An acute infusion reaction is one that meets both of the following criteria:

1. Occurs during or within 1 hour after infusion; and
2. Clinical manifestations consistent with:
    - IgE-mediated and non-IgE mediated hypersensitivity reactions, including but not limited to urticaria, skin rashes, angioedema, laryngeal edema, bronchospasm, gastrointestinal symptoms and hypotension; or
    - Cytokine release syndrome, including but not limited to fever, respiratory symptoms without the presence of wheezing, tremors, chills, flushing, pruritus, changes in blood pressure, dyspnea, chest discomfort, back pain, nausea, vomiting, diarrhea, and skin rashes.

8.2.3.2 Delayed Infusion Reaction

A delayed infusion reaction is one that meets both of the following criteria:

1. Occurs ≥1 hour after the infusion
2. Clinical manifestations as described above.

8.2.3.3 Reporting Possible and Confirmed Infusion Reactions

Possible and confirmed infusion reactions must be reported in the Infusion Reaction CRF section.

Investigators should complete the Infusion Reaction report and contact the Medical Monitor within the same timeframe as reporting SAEs, even if the infusion reaction is not an SAE. See Study Reference Manual for additional details.

8.2.4 Special Situations

Certain safety events, called 'Special Situations' that occur in association with the study drug(s) include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product

- Inadvertent or accidental exposure to the medicinal product
- Medication error involving the medicinal product (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

Special Situations will be reported to the sponsor or designated vendor within the same timeframe as SAEs on a Medication Error report form.

8.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 10 weeks after the last dose of study drug, except for pregnancy reporting (Section 8.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5).

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever is possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff.

New indications for medications started during the AE reporting period (i.e., after informed consent is obtained until 10 weeks after the last dose of study drug) will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the Investigator to meet the specified criteria.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome

- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

8.3.3 Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 4.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild**: Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; ; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death:** Fatal AE.

8.3.4 Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- **Related:**
    - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re-occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- **Not Related:**
    - The event represents a pre-existing underlying disease that has not worsened on study
    - The event has the same characteristics of a known side-effect associated with a co-medication
    - The event is an anticipated medical condition of anticipated severity for the study population
    - The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5 Reporting Serious Adverse Events on the SAE Report Form

An SAE must be reported to the Sponsor and/or its designated safety management vendor within 24 hours of becoming aware of the SAE.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

The contact information for SAE reporting is as follows:

U.S. Toll-Free Fax Number: [redacted]

Email: [redacted]

8.3.5.1 Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2 Deaths

The investigator will report the fatal or life-threatening event immediately to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to 10 weeks after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. Additionally, the site must complete the appropriate CRF page.

8.3.6 Pregnancies: Reporting and Follow-up of Subjects

The outcome of all pregnancies should be followed up and documented as described. Consent must be obtained from male subject's partner to collect information related to the pregnancy and outcome (and will be handled on a case-by-case basis with IRB/IEC approval). A Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

8.3.7 Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all laboratory results throughout the study in a timely manner, and determine whether any abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

8.3.8 Risk Management/Monitoring Programs

No specific risk management programs will be implemented.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

This study tests the hypothesis of whether FG-3019 can attenuate the annual decline in FVC in non-ambulatory DMD patients. Without treatment, the median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001). The goal of FG-3019 treatment is to reduce the annual loss to 4.5%. An enrollment of 22 subjects is planned in order to detect a reduction of 3.5% in annual FVC decline with at least 80% power, using a two sided one-sample paired t-test at a significance level of 0.05. This power calculation is based on a standard deviation of 5% and that two subjects will dropout without any efficacy assessments. A mixed-effect repeated measures model will be used in the analysis so that assessments from early dropouts will be utilized.

9.2 Analysis Populations

9.2.1 Safety Population

The Safety Population will consist of all subjects who have received any dose of FG-3019. This population is also defined as the intent-to-treat (ITT) population.

9.2.2 Full Analysis Set Population

The Full Analysis Set Population (FAS) will consist of all subjects in the Safety Population who have at least one evaluable post-baseline FVC assessment.

9.3 Statistical Analysis

9.3.1 General Considerations

Descriptive summaries will be provided for all study parameters including baseline characteristics, safety, efficacy, pharmacokinetic and pharmacodynamic parameters. Continuous variables will be reported using number of subjects, mean, standard deviation or standard error, median, minimum, and maximum. In general, standard deviation is provided to describe the distribution of a parameter, such as baseline, safety, and PK/PD parameters; while standard error is provided for efficacy analysis to facilitate between-group comparisons. Geometric mean will be included for PK/PD variables. Categorical variables will be reported by the frequency and percentage of subjects within each outcome category. Two-sided 95% confidence intervals will be presented for key efficacy parameters and two-sided 90% confidence intervals for PK/PD parameters. All statistical tests will be performed at an α=0.05 level of significance, using two-sided tests, unless otherwise stated. Assessments as well as derived parameters will be presented in data listings for all subjects in the ITT/Safety Population.

9.3.2 Subject Enrollment and Disposition

The number of subjects in each study population as well as subject completion status and reasons for early discontinuation will be summarized.

9.3.3 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 forearm MRI parameters, and quality of life parameters.

9.4 Efficacy Analyses

Efficacy analyses will be based on the FAS population. Rules of handling missing data will be described in the Statistical Analysis Plan (SAP). Analyses based on observed data will be performed for sensitivity evaluation.

9.4.1 Primary Endpoint

The primary basis for assessment of efficacy will be the capacity of FG-3019 to reduce the rate of deterioration of FVC. The primary endpoint is the difference in annual FVC (% predicted) decline during treatment with FG-3019 compared with the annual decline prior to treatment with FG-3019. The posttreatment annual change in FVC (% predicted) will be compared to that prior to treatment using a mixed effect repeated measures model (MMRM), with adjustment of baseline FVC % predicted and use of corticosteroids. Effect of age (≤16 versus >16) and effect of disease characteristics at baseline, such as time since loss of ambulation, use of ventilation, spine surgery, will be evaluated and may be included in analysis models as appropriate. The difference in annual decline rate will be presented in two-sided 95% confidence interval. Two-sided test on whether the difference is significantly from zero will be reported.

The analysis of the primary endpoint will be based on the Full Analysis Set population. For subjects who drop out of the study early, their annual change in FVC % predicted will be estimated via the combination of available assessments and the MMRM model.

Change from baseline to one year and to two years in FVC (% predicted) will be estimated via the above mentioned MMRM model. If a substantial number of subjects drop out of the study before entering Year 2 treatment, change from baseline to 2 years will be estimated only for the subset of subjects who have provided Year 2 efficacy assessment.

9.4.2 Analyses of Other PFT Parameters

Changes from baseline to 1 year and 2 years in other PFT parameters will be estimated via the above MMRM model.

9.4.3 Analysis of PUL Parameters, Pinch and Grip Strength, Brooke Scale

Change from baseline to one year and to two years in hand/arm function and strength will be estimated using the MMRM model with dominant/non-dominant side as a fixed effect and baseline value and other relevant variables as covariates. In order to evaluate overall effect, composite scores may be explored. Two-sided 95% confidence intervals will be presented.

9.4.4 Analysis of LVEF, Cardiac Fibrosis, and Forearm Fat and Fibrosis

Changes from baseline in LVEF, cardiac fibrosis, and forearm fat and fibrosis will be summarized descriptively based on available data at Year 1 and at Year 2.

9.4.5 Analysis of PODCI Quality Outcome Data

Changes from baseline in modified PODCI scores of adolescent subjects and their caregivers will be summarized descriptively based on available data at Year 1 and at Year 2. The data of adult subjects and their caregivers will be summarized separately.

9.4.6 Examination of Subgroups

Comparisons in efficacy parameters between the following subgroups may be performed. Depending on enrollment in each subgroup, grouping may be adjusted to have relatively balanced sizes.

- Age ≤16 versus age >16
- Use of corticosteroids for at least 6 months during the first year of the study versus others
- Spine surgery: yes versus no
- Different genetic characteristics
- Above and below median in years of wheel-chair bound
- Above versus below median of the baseline FVC (% predicted)
- Above versus below median of the hand and arm functional scale
- Above versus below median of the day 15 and the 6-month PK C_{min} levels
- Above versus below median of the baseline CTGF level

9.4.7 Pharmacokinetic Analyses

FG-3019 concentrations and derived PK parameters (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$) will be summarized using descriptive statistics. Pharmacokinetic analysis will be performed using commercial software such as WinNonlin.

Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters (1) in the overall population, (2) in subjects 12 to 16 years of age, and (3) in subjects older than 16 years. Comparison of PK parameters between the age groups will be performed. Trough values, measured at several time points during the course of the study, will be compared to determine steady state and accumulation.

9.4.8 Safety Analyses

Safety analyses will include summary of adverse events, prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs). In general, safety data will only be summarized descriptively and no inferential statistical procedures will be applied.

For data summarization, adverse events will be classified into standard terminology using a coding thesaurus (MedDRA), and reported by system organ class and preferred term. Treatment-emergent adverse events will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Deaths, SAEs, and AEs leading to study or treatment discontinuation, and infusion reactions will be listed or tabulated separately.

Clinically significant changes from baseline in vital signs, laboratory tests, and ECG will be identified. Shift tables will summarize changes in selected laboratory measures.

All safety analyses will be performed based on the Safety Population.

9.5 Interim and Administrative Analyses

In this open-label exploratory study, safety will be monitored on an ongoing basis and efficacy data will be evaluated periodically.

In addition to the above, a full review of efficacy and safety will be performed when PFT and other efficacy data up to and including Week 52 are available for all subjects. The study may be terminated if this review indicates that safety and efficacy endpoints will not be met after two years of treatment.

In addition, the DMC will review trends in PFTs and all other efficacy and safety data in accordance with the DMC charter.

9.6 Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will include unambiguous specifications for of all data analyses as well as documentation of changes in protocol-specified analysis plans. The SAP will describe additional study endpoints that are of interest.

10 DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the International Conference on Harmonisation (ICH) E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IVRS [or IWRS], clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The investigator must also permit the U.S. FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the investigator is notified of an inspection pertaining to this study by the U.S. FDA or other applicable regulatory authorities, the investigator must notify FibroGen immediately.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents

11.2 Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

11.3 Database Audit

A database audit will be conducted to ensure data quality and integrity.

12 ETHICS

12.1 Ethical Considerations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

12.2 Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

12.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent (ICF) and/or Assent Form from the subject or written Informed Consent Form signed by the subject's legally authorized representative, as applicable. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

12.4 Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

13 DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs/eCRFs and resolved queries.

13.2 Data Collection, Handling, and Verification

All required data will either be entered onto CRFs/eCRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with a full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion, ensuring that all data is verifiable with source documents.

14 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate document.

15 PUBLICATION POLICY

A detailed explanation of FibroGen's publication policy is described in the Clinical Trial Agreement.

16 REFERENCES

Au CG, Butler TL, Sherwood MC, Egan JR, North KN, Winlaw DS (2011) Increased connective tissue growth factor associated with cardiac fibrosis in the *mdx* mouse model of dystrophic cardiomyopathy. Int J Exp Pathol 92: (1):57-65

Bushby K, Finkel R, Birnkrant DJ, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 9: (1):77-93

Desguerre I, Mayer M, Leturcq F, Barbet JP, Gherardi RK, Christov C (2009) Endomysial fibrosis in Duchenne muscular dystrophy: a marker of poor outcome associated with macrophage alternative activation. J Neuropathol Exp Neurol 68: (7):762-773

Emery AE (1991) Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord 1: (1):19-29

Kharraz Y, Guerra J, Pessina P, Serrano AL, Munoz-Canoves P (2014) Understanding the process of fibrosis in Duchenne muscular dystrophy. Biomed Res Int **2014:**965631

Mayer OH, Finkel RS, Rummey C, et al. (2015) Characterization of pulmonary function in Duchenne Muscular Dystrophy. Pediatr Pulmonol 50: (5):487-494

McKim DA, Katz SL, Barrowman N, Ni A, LeBlanc C (2012) Lung volume recruitment slows pulmonary function decline in Duchenne muscular dystrophy. Archives of Physical Medicine and Rehabilitation 93: (7):1117-1122

Miller MR, Hankinson J, Brusasco V, et al. (2005) Standardisation of spirometry. Eur Respir J 26: (2):319-338

Morales MG, Cabello-Verrugio C, Santander C, Cabrera D, Goldschmeding R, Brandan E (2011) CTGF/CCN-2 over-expression can directly induce features of skeletal muscle dystrophy. J Pathol 225: (4):490-501

Morales MG, Gutierrez J, Cabello-Verrugio C, et al. (2013) Reducing CTGF/CCN2 slows down *mdx* muscle dystrophy and improves cell therapy. Hum Mol Genet 22: (24):4938-4951

Pessina P, Cabrera D, Morales MG, et al. (2014) Novel and optimized strategies for inducing fibrosis in vivo: Focus on Duchenne Muscular Dystrophy. Skelet Muscle 4:7

Phillips MF, Quinlivan RC, Edwards RH, Calverley PM (2001) Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med 164: (12):2191-2194

Schram G, Fournier A, Leduc H, et al. (2013) All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 61: (9):948-954

Sun G, Haginoya K, Wu Y, et al. (2008) Connective tissue growth factor is overexpressed in muscles of human muscular dystrophy. J Neurol Sci 267: (1-2):48-56

Tandon A, Villa CR, Hor KN, et al. (2015) Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. J Am Heart Assoc 4: (4):e001338

Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH (2001) Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. Arch Dis Child 84: (6):521-524

Vial C, Zuniga LM, Cabello-Verrugio C, Canon P, Fadic R, Brandan E (2008) Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. Journal of Cellular Physiology 215: (2):410-421

17 APPENDICES

Appendix 1 Schedule of Assessments: First Year of Treatment (Screening Period through Week 26)

Assessment[a]	Screening Period (4 Weeks)	Treatment Period (Weeks)													
		0	2	4	6	8	10	12	14	16	18	20	22	24	26
Informed Consent & Assent	X														
Inclusion/ Exclusion	X														
Demographics	X														
Medical History	X														
Clinical laboratory assessments[b]	X			X		X		X						X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X														X
Electrocardiogram	X														
Physical Examination[e]	X	X						X						X	
Muscle function tests[f]	X	X						X						X	
Pulmonary function tests[g]	X	X						X						X	
Cardiac MRI	X														
Forearm muscle MRI	X														
Specialty labs[h]		X	X												X
FG-3019 infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire		X													X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected prior to start, within 15 minutes of infusion completion, and within 15 minutes of completing the observation period
d. Weight to be collected in screening and every 6 months thereafter. Height (measured from ulna length) to be collected at screening and end of treatment.
e. Physical exam to include assessment of subject's ventilation use.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test
g. Pulmonary function tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details

Appendix 2 Schedule of Assessments: First Year of Treatment (Weeks 28 through 52)

Assessment[a]	Treatment Period (Weeks)												
	28	30	32	34	36	38	40	42	44	46	48	50	52
Clinical laboratory assessments[b]					X						X		
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]													X
Electrocardiogram													X
Physical Examination[e]					X						X		
Muscle function tests[f]					X						X		
Pulmonary function tests[g]					X						X		
Cardiac MRI													X
Muscle MRI (forearm)													X
Specialty labs[g]													X
FG-3019 infusion	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire													X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at screening and prior to start of infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight to be collected in screening and every 6 months thereafter. Height (measured from ulna length) to be collected at screening and end of treatment.
e. Physical exam to include assessment of subject's ventilation use.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details

Appendix 3 Schedule of Assessments: Second Year of Treatment and Post-Treatment

	Treatment Period (Weeks)										Post-Treatment
Assessment[a]	**54, 56, 58**	**60**	**62, 64, 66, 68, 70**	**72**	**74, 76, 78, 80, 82**	**84**	**86, 88, 90, 92, 94**	**96**	**98, 100, 102**	**104/ EOT**	**Week 112 ±7 days or 10 Weeks After Last Dose for Early Termination**
Clinical laboratory assessments[b]		X		X		X		X			X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]					X					X	
Electrocardiogram										X	
Physical Examination[e]		X		X		X		X		X	X
Muscle function tests[f]		X		X		X		X		X	
Pulmonary function tests[g]		X		X		X		X		X	
Cardiac MRI[h]										X	
Muscle MRI[h]										X	
Specialty labs[i]					X				X	X	X
FG-3019 infusion	X	X	X	X	X	X	X	X	X		
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire										X	

Abbreviations: EOT= end of treatment; MRI, magnetic resonance imaging, PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected prior to start of infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period
d. Weight to be collected in screening and every 6 months thereafter. Height (measured from ulna length) to be collected at screening and end of treatment.
e. Physical exam to include assessment of subject's ventilation use.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
h. The end of treatment cardiac and muscle MRIs may be performed any time from Week 104 and Week 112.
i. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details

Appendix 4 Pharmacokinetic and Pharmacodynamic Sampling Times

		Treatment Period										Post-Treatment
Sample	**Timepoint**	**Day 0**	**Day 2 ±1 day**	**Day 4 ±1 day**	**Day 7 ±1 day**	**Day 10 ±1 day**	**Week 2**	**Week 26**	**Week 52**	**Week 78**	**Week 102**	**Week 112 ±7 days or 10 Weeks After Last Dose for Early Termination**
FG-3019 PK[a]	Before infusion	X					X	X	X	X	X	
	Within 1 hour after infusion	X							X		X	
	Time point sample (no infusion)		X	X	X	X						
HAHA[b]	Predose (when applicable)	X										X
CTGF[c]	Predose (when applicable)	X										X
Exploratory[d]	Predose (when applicable)	X							X		X	X

Abbreviations: CTGF = connective tissue growth factor; HAHA = human anti-human antibody; PK = pharmacokinetic

a. Approximately 1-2 mL of blood will be collected for each measurement of FG-3019 PK.
b. Approximately 1 mL of blood will be collected for each measurement of HAHA.
c. Blood and urine samples will be collected. Approximately 1 mL of blood and 0.5 mL of urine will be collected for each measurement of CTGF.
d. Approximately 5 mL of blood will be collected for each exploratory sample.

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
PROTOCOL NUMBER:	FGCL-3019-079
PHASE:	2
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	126630
STUDY DRUG:	FG-3019
INDICATION:	Duchenne Muscular Dystrophy
FIBROGEN MEDICAL MONITOR	Name: [redacted] FibroGen, Inc. Title: [redacted] Telephone: [redacted] Mobile/Pager: [redacted] E-mail Address: [redacted]
ORIGINAL PROTOCOL:	16 June 2015
AMENDMENT 1.0	31 August 2015
AMENDMENT 2.0	06 May 2016

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy

FGCL-3019-079

Original: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen at the address provided below. Please retain the original for your study files.

Clinical Operations
FibroGen, Inc.
409 Illinois Street
San Francisco, California 94158 USA

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

This protocol is approved by FibroGen.

[redacted]

06-May-16

Date

Fi.broGen, Inc.

AMENDMENT 2.0: KEY CHANGES FROM AMENDMENT 1.0

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Key Change	Rationale	Sections Affected
Replace forearm muscle MRI with upper arm (bicep) muscle MRI.	Increased ability to detect changes in the muscle of the arm.	Synopsis, 4.1.2 Secondary Endpoints, 5.1 Inclusion Criteria, 7.1.1 Screening Period, 7.2.4 Muscle MRI, 9.3.3 Demograhics and Baseline Characteristics, 9.4.4 Analysis of LVEF, Cardiac Fibrosis, and Muscle Fat and Fibrosis, Appendix 1 Schedule of Assessments: First Year of Treatment (Screening Period through Week 26), Appendix 2 Schedule of Assessments: First Year of Treatment (Weeks 28 through 52)
Inclusion Criterion #8 revised to allow only enrollment of subjects with an FVC % predicted ≥ 50.	Improved selection of target population.	Synopsis, 5.1 Inclusion Criteria
Dosing is based on body weight measured at screening and every 3 months thereafter.	Aligning dose adjustments with body weight to be measured every 3 months.	Synopsis, 6.1.3 Preparation of Dose for Administration
Safety follow-up period reduced from 10 weeks to 4 weeks after the last dose of study drug.	Based on the half-life and known PK of FG-3019, and ICH guidelines, safety follow-up 4 weeks following the last dose of study drug is sufficient.	Synopsis, 7.1.3 End of Treatment (Per-Protocol), 7.1.4 Early Withdrawal from Treatment,7.1.5 Follow-up Period, 8.3.1 Adverse Event Reporting Period, 8.3.2 Adverse Event Eliciting/Reporting, 8.3.5.2 Deaths, Appendix 3 Schedule of Assessments: Second Year of Treatment and Post-Treatment, Appendix 4 Pharmacokinetic and Pharmacodynamic Sampling Times
Infusion rate of FG-3019 not to exceed 150 cc/hour. Adjustments to infuse at a slower rate may be made in accordance with the investigator's clinical judgment.	Avoidance of the potential for fluid overload or cardiac decompensation.	6.1.4 Administration

Key Change	Rationale	Sections Affected
Clarify the requirement for local safety labs (including hematocrit) to be drawn prior to conduct of MRIs.	Safety labs will be drawn at the site's local lab prior to any MRI to ensure there is no contraindication to MRI. Hematocrit should be included in the local lab draw as these results are required to assess fibrosis and will be provided to the central imaging vendor along with the MRI scans. Details are included in the Imaging Manual.	7.2.7 Laboratory Assessments, 7.2.7.1 Safety Assessments
Added stipulation that home health care may be considered for the administration of FG-3019 infusions during the conduct of the study in the future.	Burden of clinic visits for Q2W infusions may be challenging for non-ambulatory subjects to comply with. If deemed appropriate, home health care may be considered in the future during the conduct of this study..	6.1.4 Administration

PROTOCOL SYNOPSIS

Study Title:	Trial of FG-3019, a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
Protocol Number:	FGCL-3019-079, Amendment 2.0
Investigational Product:	FG-3019 (Recombinant fully human IgG_1 kappa monoclonal antibody to connective tissue growth factor)
Study Phase:	Phase 2
Target Population:	Non-ambulatory subjects with Duchenne muscular dystrophy (DMD)
Number of Subjects Planned:	Approximately 22
Study Centers Planned:	Approximately 10 centers

OBJECTIVES

Primary Objective

To estimate FG-3019's efficacy in non-ambulatory subjects with DMD

Secondary Objectives

1. To evaluate safety and tolerability of FG-3019 administered intravenously every 2 weeks
2. To assess pharmacokinetics of FG-3019 in the targeted pediatric population
3. To evaluate pharmacodynamic markers of FG-3019's effects in DMD

ENDPOINTS/ASSESSMENTS

Efficacy

Primary Endpoint

- Difference in annual forced vital capacity (FVC) (% predicted) decline during treatment of FG-3019 compared with the estimated annual decline prior to FG-3019 treatment.

Secondary Endpoints

- Change from baseline to 1 year in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow

- Change in LVEF from baseline to 1 year
- Change from baseline to 1 year in Performance of Upper Limb (PUL) Score
- Change from baseline to 1 year in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to 1 year in cardiac fibrosis score assessed by magnetic resonance imaging (MRI)
- Change from baseline to 1 year in upper arm (bicep) muscle fat and fibrosis assessed by MRI
- Changes from baseline to 2 years in the efficacy parameters

Exploratory, Pharmacokinetics, Pharmacodynamics

- Pharmacokinetic (PK) profile of FG-3019 (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$)
  - In the overall population
  - In subjects 12 to 16 years of age, inclusive
  - In subjects older than 16 years
  - Comparison of PK profiles across age groups
- Plasma and urine connective tissue growth factor (CTGF)
- Creatine kinase (CK)
- Circulating biomarkers

Safety

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

STUDY DESIGN

This study will be an open-label, single arm study of approximately 22 subjects. Each subject will receive FG-3019 (35 mg/kg, every 2 weeks) for 2 years. All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow). An interim analysis of safety and efficacy will be performed after all evaluable subjects complete one year of dosing.

If this analysis indicates a potential benefit, treatment will be continued through Week 102 to determine the further course of any trends in efficacy and safety parameters observed after 52 weeks of treatment.

STUDY PROCEDURES

Details regarding study procedures are provided as follows:

Appendix 1: Screening Period through Week 26

Appendix 2: Week 28 through Week 52

Appendix 3: Year 2 and Post-Treatment

Appendix 4: Pharmacokinetic and Pharmacodynamic Sampling Times

MAIN SELECTION CRITERIA

Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory; wheelchair dependent for <5 years
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC ≥ 50
9. Estimated annual decline of FVC (% predicted) of ≥5% based upon at least 2 PFTs done in the previous 18 months, in addition to the screening FVC
10. Left ventricular ejection fraction >45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Stable regimen of heart failure cardiac medications (e,g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation.
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >10 g/dL
    c. Absolute neutrophil count >1000/mcL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤2x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after last dose of study drug.

Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 2 years of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 1 year
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug within 28 days prior to start of study treatment
11. Ongoing participation in any other therapeutic clinical trial. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

TREATMENTS

FG-3019 Dose, and Mode of Administration

Each subject will receive FG-3019 (35 mg/kg, every 2 weeks) for 2 years. The dose of FG-3019 (35 mg/kg) for each infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken every 3 months thereafter.

Reference Therapy: Not applicable

Concomitant Medications/Therapies: Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy. Investigational agents and currently investigational agents that receive marketing authorization during this trial are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed. Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

STATISTIC METHODS

This study will enroll approximately 22 subjects. A sample size of 22 subjects will provide 84% power to detect an absolute difference of 3.5% in FVC % predicted, using a two-sided, one-sample paired t-test to compare the annual change posttreatment with that prior to treatment at significance level 0.05. This calculation is based on assumption of standard deviation of 5% and assumption of two dropouts without any efficacy

assessments at study completion.

The primary basis for assessment of efficacy will be the capacity of FG-3019 to reduce the rate of deterioration of FVC. The primary endpoint is the difference in annual FVC (% predicted) decline during treatment with FG-3019 compared with the annual decline prior to treatment with FG-3019. The posttreatment annual change in FVC (% predicted) will be compared to that prior to treatment using a mixed effect repeated measures model (MMRM), with adjustment of baseline FVC % predicted and use of corticosteroid. Effect of age (≤16 versus >16) and effect of disease characteristics at baseline, such as time since loss of ambulation, use of ventilation, spine surgery, type of genetic mutation, will be evaluated and may be included in analysis models as appropriate. The difference in annual decline rate will be presented in two-sided 95% confidence interval. Two-sided test on whether the difference is significantly different from zero will be reported.

The analysis of the primary endpoint will be based on the Full Analysis Set population. For subjects who drop out of the study early, their annual change in FVC % predicted will be estimated via the combination of available assessments and the MMRM model.

Change from baseline to one year and to two years in FVC (% predicted) will be estimated via the above mentioned MMRM model. If a substantial number of subjects drop out of the study before entering Year 2 treatment, change from baseline to 2 years will be estimated only for the subset of subjects who have provided Year 2 efficacy assessment.

Summary statistics for observed values, change from baseline, and percent change from baseline will be reported for all secondary endpoints. For those secondary outcomes where historical data is available, the effect of FG-3019 may be investigated further by performing repeated measures analyses.

FG-3019 concentrations and derived PK parameters will be tabulated and summarized using descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters. Attainment of steady-state will be investigated.

Safety analyses will include summary of adverse events (including treatment emergent AEs, treatment emergent serious AEs, deaths, and infusion-associated AEs), prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs), and physical exams.

TABLE OF CONTENTS

LIST OF APPENDICES

2 BACKGROUND

2.1 Description of FG-3019

FG-3019 is a recombinant fully human immunoglobulin G_1 (IgG) kappa monoclonal antibody to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role. These diseases include liver fibrosis due to hepatitis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne muscular dystrophy (DMD). FG-3019 (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. FG-3019 contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2 Duchenne Muscle Dystrophy

Duchenne muscular dystrophy (DMD) is usually inherited in an X-linked recessive fashion, but it can occur as a result of spontaneous mutation in boys from families without a known history of the condition. On the basis of some 40 studies including several million male births, incidence at birth of Duchenne muscular dystrophy is around 1:3300, and its prevalence in the population (in terms of the total male population) is around 1:16500 (Emery, 1991).

DMD is a result of mutations (mainly deletions) in the dystrophin gene (DMD; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration with loss of independent ambulation by the age of 13 years (Bushby, 2010).

In skeletal muscles of DMD patients constant myofiber breakdown results in persistent activation of myofibroblasts and altered production of extracellular matrix (ECM) resulting in extensive fibrosis. Muscle fibrosis is the only myo-pathologic parameter that significantly correlated with poor motor outcome as assessed by quadriceps muscle strength, manual muscle testing of upper and lower limbs, and age at ambulation loss (Desguerre, 2009).

Patients with DMD are generally wheelchair bound before they develop significant respiratory muscle weakness. Respiratory complications are the primary cause of morbidity and mortality in DMD as progressive respiratory muscle weakness leads to hypoventilation and/or recurrent atelectasis and pneumonia, secondary to decreased cough effectiveness (McKim, 2012).

After age 10 to 14, patients gradually begin to lose respiratory muscle function based on pulmonary function tests (PFTs) such as forced vital capacity (FVC). The median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001, Tangsrud, 2001).

Because of improvements in respiratory care, cardiac dysfunction is now a leading cause of morbidity and mortality in DMD patients (Schram, 2013). Progressive myocardial fibrosis, as detected by late gadolinium enhancement (LGE), is strongly correlated with the left ventricular ejection fraction (LVEF) decline in Duchenne muscular dystrophy patients. Longer steroid treatment duration is associated with a lower age-related increase in myocardial fibrosis burden (Tandon, 2015).

2.2.1 Relevance of Connective Tissue Growth Factor (CTGF) in DMD

Connective tissue growth factor (CTGF) is a nonstructural regulatory protein present in the extracellular matrix that has an important role in fibrosis. Skeletal muscle from DMD patients, dystrophic dogs, and mdx mice all show elevated levels of CTGF (Sun, 2008).

CTGF can reproduce or amplify the effects of TGFβ on fibrosis by inducing collagen type 1, α5 integrin, and fibronectin much more potently than TGFβ in fibroblasts (Kharraz, 2014).

Comparison of mdx mice with normal or genetically depleted levels of CTGF revealed that exercised mice with reduced CTGF developed less fibrosis and exhibited better muscle strength than mice with normal levels of CTGF (Morales, 2013). In culture, both myoblasts and myotubes were shown to express and secrete CTGF to the medium, and respond to the growth factor by increasing the extracellular matrix constituents, partially inhibiting myoblasts differentiation and inducing myoblasts dedifferentiation (Vial, 2008).

In DMD, the role of CTGF might extend well beyond replacement fibrosis secondary to loss of muscle fibers, since its overexpression in skeletal muscle could by itself induce a dystrophic phenotype (Morales, 2013).

A major feature of the hearts of DMD patients is cardiac fibrosis. Cardiac fibrosis is associated with increased CTGF expression in the *mdx* mouse heart. CTGF may be a key mediator of early and persistent fibrosis in dystrophic cardiomyopathy (Au, 2011).

CTGF is critically involved in several chronic fibro-degenerative diseases. FG-3019 treatment has been shown to positively the affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.

2.3 A Summary of Relevant Findings from Nonclinical Studies and from Clinical Trials

Please refer to the most recent version of FG-3019 Investigator's Brochure.

2.3.1 Nonclinical Studies

In DMD, the genetic loss of the cytoskeletal protein dystrophin results in muscle damage that, leads to progressive replacement of muscle with fibrotic and fat tissue. This progressive muscle damage can be recapitulated in the DMD mouse model (*mdx*), and accelerated by muscle usage (Pessina, 2014).

As was observed with genetic depletion of CTGF, pharmacologic inhibition of active CTGF in *mdx* mice by treatment with FG-3019 resulted in reduced fibrosis and skeletal muscle damage, as well as improved preservation of skeletal muscle strength in isolated muscles. The FG-3019 treated *mdx* mice were also subjected to a test of exercise endurance, in which they showed better performance than *mdx* mice injected with control IgG (Morales, 2013).

FG-3019 treatment of *mdx* mice was associated with decreased skeletal muscle damage and fibrosis, decreased collagen III and fibronectin expression, decreased plasma creatine kinase (CK) (Morales, 2013), and increased isometric force of skeletal muscle (Morales, 2011).

2.3.2 Pharmacokinetics

Key findings are summarized below from Phase 1 and 2 studies investigating the pharmacokinetics (PK) of FG-3019 in subjects with diabetic kidney disease, idiopathic pulmonary fibrosis, and pancreatic cancer:

- FG-3019 was administered over the dose range of 3 to 45 mg/kg every 2 weeks and 17.5 to 22.5 mg/kg weekly.
- FG-3019 exposure (e.g., mean/median C_{max} and C_{min}, area under the curve [AUC]) generally increased with increasing dose.
- The $t_{1/2}$ was approximately 1 to 2 weeks at doses >25 mg/kg in a trial in pancreatic cancer subjects.

2.3.3 Safety

Key findings are summarized below from the Phase 1 and 2 studies involving more than 400 adults with diabetic kidney disease, idiopathic pulmonary fibrosis, and liver fibrosis due to hepatitis B or pancreatic cancer:

- Overall, FG-3019 was well tolerated across the range of doses noted above, and there were no dose-limiting toxicities.
- Treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity and transient in duration.
- Infusion-related reactions have been mild-to-moderate and did not recur following re-administration of FG-3019
- TEAEs were considered typical of the subjects' underlying medical condition(s) and, in the placebo-controlled studies, were equally distributed between placebo and FG-3019 treatment groups.
- No apparent pattern to TEAEs that occurred within 24 hours after infusions was observed.
- No apparent pattern for treatment-emergent serious adverse events (TESAEs) was observed during clinical testing.

2.3.4 Efficacy

Key efficacy findings are summarized below from the Phase 1 and 2 studies of CTGF inhibition by FG-3019 in indications other than DMD.

2.3.4.1 Pancreatic Cancer

Biweekly doses of up to and including 45 mg/kg and weekly doses of 17.5 and 22.5 mg/kg were administered to subjects with previously untreated locally advanced or metastatic pancreatic adenocarcinoma. Increased exposure to FG-3019 was associated with increased survival. There appears to be a relationship between survival and trough blood levels of FG-3019 (C_{min}). Notably C_{min} >150 mcg/mL after the first dose of FG-3019 (Day 15) was associated with significantly increased progression free survival and overall survival.

A maximal effect in survival benefit was achieved at dose levels of 25 to 45 mg/kg/2 weeks.

2.3.4.2 Idiopathic Pulmonary Fibrosis (IPF)

In subjects with IPF who completed 45 weeks of dosing with 15 or 30 mg/kg FG-3019, approximately 40% of subjects had stable or improved lung fibrosis by quantitative high resolution CT imaging compared to baseline values with approximately 30% having improved pulmonary fibrosis.

Overall, subjects with stable or improved lung fibrosis also had stable or improved FVC (% predicted).

2.4 Risks and Benefits

FG-3019 has been generally well tolerated with most adverse events being typical of those expected for subjects with the underlying disease conditions.

Infusion-related reactions have been rarely observed in some subjects treated with FG-3019. Across studies in other indications, infusion-related reactions have been mild-to-moderate did not result in discontinuation of treatment with FG-3019, and did not result in the use of prophylaxis for subsequent infusions.

The favorable experience with FG-3019 to date does not exclude the possibility of more severe infusion reactions occurring in future subjects.

This is the first clinical study of FG-3019 in DMD. There are currently no confirmed benefits to subjects with DMD treated with FG-3019. However, a potential benefit of treatment with FG-3019 is indicated in preclinical models of DMD and previous clinical studies of FG-3019 in other indications where CTGF is also associated with disease progression.

Dose regimens equal to or exceeding 35 mg/kg have been implemented in other indications in adult subjects. The objective of these studies was to inhibit bioactive CTGF, which is associated with disease progression in a number of indications. Please refer to the Investigator's Brochure for a comprehensive summary of efficacy, safety, and exposure data.

The current study will explore the clinical relevance of CTGF inhibition, as indicated in preclinical models, in DMD patients.

2.5 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Periods

FG-3019 is administered as an IV infusion at a dose of 35 mg/kg every two weeks for two years (Day 0 to Week 102). The dose, frequency and route of administration correspond with dose regimens that were well tolerated and possibly associated with efficacy in clinical studies in adults with IPF and pancreatic cancer. In both of these indications FG-3019 was administered at doses that included the targeted dose regimen for the current study (35 mg/kg bodyweight) and greater (45 mg/kg bodyweight). These doses were not associated with dose limiting toxicity.

The overall objective of all of these studies, including the current study, is to provide a dose associated with clinically relevant CTGF blockade to impede progression of serious disease states. Body weight-related dosing and utilization of a dose no greater than the maximal dose used in adults are expected to ensure that systemic exposure in the targeted pediatric population will not exceed the systemic exposure achieved in adults.

PK assessments will be done during the course of the study and facilitate ongoing monitoring of exposure to FG-3019 during the course of the study.

The planned treatment duration is no longer than total treatment periods achieved in previous studies with FG-3019.

The duration of treatment of the current study is also similar to the duration of other studies in DMD and is expected to provide sufficient basis to evaluate potential benefit in the targeted pediatric population with DMD.

2.6 Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents. Detailed information regarding study conduct is found in Sections 10, 11, 12, and 13.

2.7 Population to be Studied

Non-ambulatory adolescents and adults with DMD will be enrolled in this trial.
A detailed inclusion/exclusion list is provided in Section 5.

3 OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is to estimate FG-3019's efficacy in non-ambulatory subjects with DMD.

3.2 Secondary Objectives

The following are the secondary objectives of this trial:

1. To evaluate safety and tolerability of FG-3019 administered intravenously every 2 weeks
2. To assess pharmacokinetics of FG-3019 in the targeted pediatric population
3. To evaluate pharmacodynamic markers of FG-3019's effects in DMD

4 STUDY DESIGN

4.1 Endpoints and Assessments

4.1.1 Primary Endpoint

The primary endpoint is the difference in annual forced vital capacity (FVC) (% predicted) decline during treatment of FG-3019 compared with the estimated annual decline prior to FG-3019 treatment.

4.1.2 Secondary Endpoints

The following are the secondary endpoints:

- Change from baseline to 1 year in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow
- Change in LVEF from baseline to 1 year
- Change from baseline to 1 year in Performance of Upper Limb (PUL) Score
- Change from baseline to 1 year in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to 1 year in cardiac fibrosis score assessed by MRI
- Change from baseline to 1 year in upper arm (bicep) muscle fat and fibrosis assessed by MRI
- Changes from baseline to 2 years in the efficacy parameters

4.1.3 Exploratory, Pharmacokinetic and Pharmacodynamic Outcome Measures

Exploratory outcome measures for this trial are:

- Pharmacokinetic (PK) profile of FG-3019 (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$)
    - In the overall population
    - In subjects 12 to 16 years of age, inclusive
    - In subjects older than 16 years
    - Comparison of PK profiles across age groups
- Plasma and urine CTGF
- Creatine kinase (CK)
- Circulating biomarkers

4.1.4 Safety Assessments

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

4.2 Trial Overview

This study will be an open-label, single arm study of approximately 22 subjects. Each subject will receive FG-3019 (35 mg/kg, every 2 weeks) for up to 2 years. All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow) on a continuous basis.

An interim analysis of safety and efficacy will be performed after all evaluable subjects complete one year of dosing. If this analysis indicates a potential positive benefit/risk, the treatment will continue through Week 102 to determine the further course of any trends in efficacy parameters observed after 52 weeks of treatment. Upon completion of treatment or premature discontinuation from the trial, subjects will be asked to return to the investigative site to complete final safety and efficacy assessments.

4.3 Study Treatment

4.3.1 Dose and Schedule

Each subject will receive FG-3019 (35 mg/kg) intravenously every 2 weeks (q2w). See Section 6 for detailed information on study drug formulation, storage, and administration.

4.3.2 Rationale for Dose and Schedule

The FG-3019 dose is based on results of a study in adult subjects with pancreatic cancer. In that study (Section 2.3.4.1), minimum FG-3019 blood levels (C_{min}) ≥150 mcg/mL were associated with increased median survival and 1 year survival compared to subjects with C_{min} <150 mcg/mL. Given the apparent threshold effect for increased benefit when minimal FG-3019 exposure is ≥150 mcg/mL and based on PK analysis using these data, the planned dose of 35 mg/kg administered every 2 weeks is projected to achieve this minimum exposure in the targeted DMD study population.

4.4 Concomitant Medications, Procedures and Nondrug Therapies

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy.

Investigational agents and investigational agents that receive marketing authorization during this trial are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

Concomitant medications (any prescription and/or over-the-counter [OTC] preparation) and procedures or nondrug therapies (e.g., physical therapy or acupuncture) used by a subject while participating in this clinical trial must be recorded from the Screening Visit through the End-of-Study Visit.

Questions regarding potential impact of concomitant medications on evaluability of subjects enrolled in the study should be addressed to the attention of the FibroGen Medical Monitor or designee.

4.4.1 Contraception

Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy of a partner must be reported (Section 8.3.6).

4.5 Safety Plan

An ongoing safety review is facilitated by the unblinded nature of the study. FibroGen will review safety data and will communicate the results of these reviews to investigators by email or teleconference on a regular basis. In addition, FibroGen will review safety experience with investigators during teleconferences that will be held at least quarterly and include the conclusions of the Data Monitoring Committee's (DMC) latest data review.

FibroGen will notify investigators immediately if a new safety risk is identified.

4.6 Data Monitoring Committee

A DMC will be utilized and will be composed of external and internal (FibroGen) experts. Composition and responsibilities of the DMC are defined in a separate DMC charter.

DMC responsibilities include review of safety data, available pharmacokinetic data, and pulmonary function tests.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory; wheelchair dependent for <5 years
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC ≥ 50
9. Estimated annual decline of FVC (% predicted) of ≥5% based upon at least 2 PFTs done in the previous 18 months, in addition to the screening FVC
10. Left ventricular ejection fraction >45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Stable regimen of heart failure cardiac medications (e,g, angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >10 g/dL
    c. Absolute neutrophil count >1000/mcL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤2x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after the last dose of study drug

5.2 Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 2 years of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 1 year
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug within 28 days prior to start of study treatment
11. Ongoing participation in any other therapeutic clinical trial. Use of deflazacort if regarded by the principal investigator as standard of care is allowed

5.3 Subject Withdrawal

Subjects may withdraw from the study at any time.

The investigator will remove a subject from study treatment for the following reasons:

- Adverse events, which in the opinion of the Principal Investigator and/or FibroGen preclude further study drug dosing
- Nonadherence to protocol-defined procedures, in particular missing of 3 or more sequential study drug infusions
- Not available for safety assessments

Subjects who discontinue the study early should be strongly encouraged to complete the evaluations described in Section 7.1.3.

5.4 Replacement of Subjects

Subjects may be replaced in this study if a subject's participation is not terminated due to safety or tolerability issues and is replaced prior to completion of targeted recruitment of approximately 22 subjects into the study. Replacement decisions will be made between the sponsor and investigator on a case-by-case basis.

5.5 Study Termination

This trial can be terminated by the sponsor at any time for any reason.

6 STUDY DRUG/TREATMENT SUPPLY

6.1 FibroGen Investigational Product

FG-3019 is a fully human IgG_1 kappa monoclonal antibody that binds to CTGF.

6.1.1 Formulation

FG-3019 is supplied in single-use glass vials containing 10 mL of a sterile, preservative-free solution. The solution is composed of 10 mg/mL FG-3019, 1.60 mg/mL l-histidine, 3.08 mg/mL l-histidine HCl, 8.01 mg/mL sodium chloride and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0.

6.1.2 Storage

Vials of FG-3019 must be stored refrigerated (2°C to 8°C), in a temperature-controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation.

6.1.3 Preparation of Dose for Administration

The dose of FG-3019 (35 mg/kg) for each infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken every 3 months thereafter. FG-3109 may be administered undiluted or, for convenience of infusion, may be diluted with 0.9% Sodium Chloride Injection according to the Dose Preparation Instructions in the Study Reference Investigational Product (IP) Manual.

FG-3019 will be administered as soon as possible after release from the site's pharmacy and within 24 hours of preparation. FG-3019 will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

6.1.4 Administration

Study Drug	Dose	Route	Infusion Rate	Schedule
FG-3019	35 mg/kg	IV	Not to exceed 150 cc/hour	Every 2 weeks
DO NOT ADMINISTER FG-3019 AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.				

For this study, the overall rate of infusion for the prepared study drug should not exceed 150 cc/hour. Adjustments may be made to further slow the rate of infusion (infusing less than 150 cc/hour) in accordance with the investigator's clinical judgement. Subjects should be carefully monitored for reaction during the first infusion with a physician available as needed. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation. The IV access should remain in place and be maintained per site procedures until the end of this posttreatment observation period.

If a subject has an infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences an infusion reaction and continues FG-3019 dosing, a physician must be immediately available during subsequent infusions and observation periods until the subject does not have any infusion reaction for three sequential infusions.

Premedication, such as antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are not normally administered before infusions of FG-3019. Premedication may be used for subjects who experience infusion reactions at the discretion of the investigator after discussion with the Medical Monitor.

FG-3019 will be administered in a hospital or ambulatory setting with adequate facilities for managing medical emergencies for at least three infusions to confirm the subject does not have an infusion reaction. The study site must have trained staff and medications for the treatment of acute reactions, including anaphylaxis, immediately available. There is no specific treatment for an FG-3019 overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

FibroGen may consider the use of properly trained home health care staff to administer the FG-3019 infusions in the future and corresponding study assessments during the conduct of the study, consistent with institutional regulations and policies.

7 ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

7.1 Study Procedures by Visit

All study procedures and assessments will be performed in accordance with the Schedule of Assessments presented in Appendix 1 (Screening Period through Week 26), Appendix 2 (Weeks 28 through 52), Appendix 3 (Second Year of Treatment and Post-Treatment Assessments), and Appendix 4 (Pharmacokinetic and Pharmacodynamic Sampling Times).

For all potential subjects, screening procedures required to determine subject eligibility will be performed within 28 days prior to Day 0 (first infusion of FG-3019). Potential subjects may be re-screened if initial screening procedures lie outside the 28-day screening period prior to planned study entry.

Subject's eligibility for this study will be reviewed and approved by Sponsor's medical monitor prior to subject enrollment.

The following assessments are relevant to the assessment of efficacy: pulmonary function tests (FVC, mean inspiratory flow (MIF), peak expiratory flow), Brooke Upper Extremity Rating Scale, Performance of the Upper Limb, pinch strength, grip strength, cardiac MRI, and muscle MRI. Refer to the Study Reference Manual for details.

Approved windows for performing study assessments are defined in the following sections.

7.1.1 Screening Period (no earlier than Day -28)

Assessments to be conducted during the screening period are presented in Appendix 1.

Screening assessments may be completed over several visits during the screening period. It is recommended that the less invasive screening assessments be performed first upon completion of the signed Informed Consent and/or Assent Form [ICF] (demographics, medical history, blood draws, electrocardiogram [ECG], vital signs (includes body weight and height), physical exam, pulmonary function tests (PFTs), and then followed by the more rigorous screening assessments (i.e., muscle function tests, cardiac MRI).

A cardiac MRI performed within 3 months prior to Day 0 (start of dosing) is acceptable to confirm eligibility based on the LVEF study entry criterion and as baseline cardiac MRI. If an historic MRI is not available, a cardiac MRI must be performed during the Screening Period.

An upper arm muscle MRI is not required to determine subject eligibility at screening, but may be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Muscle and pulmonary function tests (PFTs) will be performed during the screening period. Muscle function and PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.

In addition, an exploratory blood sample will be drawn for analysis of circulating biomarkers of fibrosis and specific muscle miRNAs (dystromirs) prior to first FG-3019 infusion.

7.1.2 Dosing Period

The dosing period begins on the first day of dosing with study treatment (Day 0) and continues through Week 102. Subjects will receive study drug every 2 weeks.

The visit window for all dosing visits is ±2 days. Visits should be scheduled based on the the previous visit, not the baseline visit.

Assessments and procedures to be performed during the dosing period are presented in Appendix 1 (Screening Period through Week 26), Appendix 2 (Weeks 28 through 52), and Appendix 3 (Second Year of Treatment and Post-Treatment).

Muscle or pulmonary function tests that cannot be performed or produce inadequate results according to test procedures during a specified visit should be performed by the next scheduled dosing visit.

Both cardiac and muscle MRIs may be performed within ±2 weeks of the specified visit.

Blood samples will be drawn for pharmacokinetic analysis according to the schedule in Appendix 4. Blood draws to be collected on non-dosing days may be collected within ±1 day as outlined in Appendix 4.

7.1.3 End of Treatment (Per-Protocol)

Assessments and procedures to be conducted after the last dose of study drug are presented in Appendix 3.

The end of treatment cardiac and muscle MRIs may be performed any time from Week 104 to Week 106.

7.1.4 Early Withdrawal from Treatment

Subjects who prematurely discontinue the study should be strongly encouraged to complete the follow-up period, including; the final efficacy evaluations scheduled for Week 104 and the safety follow-up evaluations scheduled for Week 106 (about 4 weeks following the last dose).

7.1.5 Follow-Up Period

The follow-up period begins when subjects complete Year 2 efficacy evaluations at Week 104, or at premature study termination. For all subjects, the final safety assessments should be completed 4 weeks (±7 days) after the last dose of FG-3019.

7.1.6 Missed Visits

Every attempt must be made to complete all study visits as outlined in the Schedules of Assessments. Missed infusions will not be replaced. If a subject misses a scheduled efficacy assessment, the assessment should be performed as soon after the missed visit as feasible and within the windows specified above.

7.1.7 Unscheduled Visits

Unscheduled Visit assessments may be required at the discretion of the investigator.

7.2 Assessments

Please refer to the Schedules of Assessments (Appendix 1, Appendix 2, Appendix 3, and Appendix 4) for the scope and timing of assessments. Please refer to the Laboratory Manual for details regarding laboratory sample collection and processing; and the Study Reference Manual for details regarding the conduct of functional tests and MRIs.

7.2.1 Pulmonary Function Tests

The following pulmonary function tests (PFTs) will be performed to assess changes in lung function: forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow rate (PEF; PEFR), forced expiratory volume in 1 second (FEV1), and peak cough flow (Mayer, 2015, Miller, 2005).

7.2.2 Muscle Strength and Functional Measurements

The following assessments will be performed to assess changes in upper extremity strength and function: Brooke Upper Extremity Rating Scale (Brooke Scale), Performance of the Upper Limb (PUL), Grip Test, and Pinch Strength Test.

7.2.3 Cardiac MRI

Cardiac MRIs, will be performed during screening and at yearly intervals to assess changes in left ventricular ejection fraction (LVEF) and presence of late gadolinium enhancement (LGE), a marker for myocardial fibrosis.

7.2.4 Muscle MRI

Upper arm (bicep) muscle MRIs will be performed at Day 0 and at yearly intervals to assess changes in degree of fatty replacement of select muscle groups by T2 relaxation time mapping.

7.2.5 Quality of Life Questionnaire

Pediatrics Outcomes Data Collection Instrument (PODCI) Quality Outcome Questionnaire will be performed to assess if treatment with FG-3019 improves quality of life.

7.2.6 Vital Signs and Physical Examinations

A physical examination will be performed at screening and baseline (Day 0), every 12 weeks and at end of treatment and post-treatment follow-up. Examinations in screening, Week 52 (±2 weeks) and Week 104 (±2 weeks) should be complete examinations. Other examinations may be disease-specific or problem-oriented examinations.

Vital signs (pulse, respiration, sitting blood pressure, and temperature) will be collected at screening and prior to start of each infusion, within 15 minutes of the end of each infusion, and within 15 minutes of the completion of the post-infusion observation period.

7.2.7 Laboratory Assessments

All laboratory tests of blood and/or urine specimens will be performed at a central laboratory or FibroGen, as appropriate. A Central Laboratory Manual with instructions

on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local clinical laboratories will be used to assess and facilitate the management of adverse events and to provide usual standard of care (including blood draws required prior to MRIs). Local clinical laboratory data will not be collected in the study database except for hematocrit values provided with with imaging data.

7.2.7.1 Safety Assessments

Blood samples will be 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.

Safety labs will be drawn at the site's local lab prior to MRIs to ensure there is no contraindication to MRI. Hematocrit should be included in the local lab draw as these results are required to assess fibrosis and will be provided to the central imaging vendor along with the MRI scans. Details are included in the Imaging Manual.

7.2.7.2 Pharmacokinetics

Plasma concentrations of FG-3019 will be determined on Day 0 pre-dose and within 1 hour post infusion, then on Days 2, 4, 7, 10, and 14. The Day 14 sample should be on the same day of, but prior to the start of the next infusion of study drug.

Day 2, 4, 7, and 10 PK assessments represent target days following the first dose; however, actual sample collection time of up to ±1 day of the target time is acceptable as long as the actual time of dosing and actual time of each sample collection are recorded accurately.

At Weeks 26, 52, 78, and 102, trough FG-3019 levels (C_{min}) will be determined prior to study drug infusion.

PK samples will also be drawn within 60 minutes of infusion completion on Weeks 52 and 102.

7.2.7.3 Plasma and Urine CTGF

Plasma and urine samples will be analyzed for CTGF concentrations from samples taken as described in Appendix 4.

7.2.7.4 HAHA

Blood samples will be drawn for analysis of human anti-human antibody (HAHA) according to the schedule in Appendix 4.

7.2.7.5 Biomarkers

Blood samples will be drawn for analysis of biomarkers. The exact biomarkers will be based on current scientific knowledge regarding CTGF, FG-3019 and DMD at the time the tests are performed. No genetic testing will be performed.

8 ASSESSMENT OF SAFETY

8.1 Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 1 (Screening Period through Week 26), Appendix 2 (Weeks 28 through 52), and Appendix 3 (Second Year of Treatment and Post-Treatment). In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the Study Drug.

8.2 Definitions

8.2.1 Definition of an Adverse Event (AE)

For the purpose of this study, an AE is any untoward medical occurrence that occurred in the protocol-specified AE reporting period, and which does not necessarily have a causal relationship with the study drug. An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.3.1).

8.2.2 Definition of a Serious Adverse Event (SAE)

A **serious adverse event** is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.2.3 Definition of an Infusion Reaction

Infusion reactions are immunologic reactions to an infused protein, and are different from events resulting from the process of infusing the protein (e.g., infusion site bruise) and are different from adverse events due to the infused protein's intended or unintended pharmacologic effects.

8.2.3.1 Acute Infusion Reaction

An acute infusion reaction is one that meets both of the following criteria:

1. Occurs during or within 1 hour after infusion; and
2. Clinical manifestations consistent with:
    - IgE-mediated and non-IgE mediated hypersensitivity reactions, including but not limited to urticaria, skin rashes, angioedema, laryngeal edema, bronchospasm, gastrointestinal symptoms and hypotension; or
    - Cytokine release syndrome, including but not limited to fever, respiratory symptoms without the presence of wheezing, tremors, chills, flushing, pruritus, changes in blood pressure, dyspnea, chest discomfort, back pain, nausea, vomiting, diarrhea, and skin rashes.

8.2.3.2 Delayed Infusion Reaction

A delayed infusion reaction is one that meets both of the following criteria:

1. Occurs ≥1 hour after the infusion
2. Clinical manifestations as described above.

8.2.3.3 Reporting Possible and Confirmed Infusion Reactions

Both acute and delayed infusion reactions will be captured as AEs and also be reported to the medical monitor within 24 hours. See Study Reference Manual for additional details.

8.2.4 Special Situations

Certain safety events, called 'Special Situations' that occur in association with the study drug(s) include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product

- Medication error involving the medicinal product (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

Special Situations will be reported to the sponsor or designated vendor within 24 hours on a Medication Error report form. See Study Reference Manual for details.

8.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 4 weeks after the last dose of study drug, except for pregnancy reporting (Section 8.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5).

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever is possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff.

New indications for medications started during the AE reporting period (i.e., after informed consent is obtained until 4 weeks after the last dose of study drug) will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the Investigator to meet the specified criteria.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug

- Other treatment required
- Determination of "seriousness"

8.3.3 Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 4.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild**: Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; ; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death:** Fatal AE.

8.3.4 Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- **Related:**
    - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re-occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- **Not Related:**
    - The event represents a pre-existing underlying disease that has not worsened on study
    - The event has the same characteristics of a known side-effect associated with a co-medication
    - The event is an anticipated medical condition of anticipated severity for the study population
    - The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5 Reporting Serious Adverse Events on the SAE Report Form

An SAE must be reported to the Sponsor and/or its designated safety management vendor within 24 hours of becoming aware of the SAE.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

The contact information for SAE reporting is as follows:

U.S. Toll-Free Fax Number: [redacted]

Email: [redacted]

8.3.5.1 Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2 Deaths

The investigator will report the fatal or life-threatening event immediately to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to 4 weeks after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. Additionally, the site must complete the appropriate CRF page.

8.3.6 Pregnancies: Reporting and Follow-up of Subjects

The outcome of all pregnancies should be followed up and documented as described. Consent must be obtained from male subject's partner to collect information related to the pregnancy and outcome (and will be handled on a case-by-case basis with IRB/IEC approval). A Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

8.3.7 Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all laboratory results throughout the study in a timely manner, and determine whether any abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

8.3.8 Risk Management/Monitoring Programs

No specific risk management programs will be implemented.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

This study tests the hypothesis of whether FG-3019 can attenuate the annual decline in FVC in non-ambulatory DMD patients. Without treatment, the median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001). The goal of FG-3019 treatment is to reduce the annual loss to 4.5%. An enrollment of approximately 22 subjects is planned in order to detect a reduction of 3.5% in annual FVC decline with at least 80% power, using a two sided one-sample paired t-test at a significance level of 0.05. This power calculation is based on a standard deviation of 5% and that two subjects will dropout without any efficacy assessments. A mixed-effect repeated measures model will be used in the analysis so that assessments from early dropouts will be utilized.

9.2 Analysis Populations

9.2.1 Safety Population

The Safety Population will consist of all subjects who have received any dose of FG-3019. This population is also defined as the intent-to-treat (ITT) population.

9.2.2 Full Analysis Set Population

The Full Analysis Set Population (FAS) will consist of all subjects in the Safety Population who have at least one evaluable post-baseline FVC assessment.

9.3 Statistical Analysis

9.3.1 General Considerations

Descriptive summaries will be provided for all study parameters including baseline characteristics, safety, efficacy, pharmacokinetic and pharmacodynamic parameters. Continuous variables will be reported using number of subjects, mean, standard deviation or standard error, median, minimum, and maximum. In general, standard deviation is provided to describe the distribution of a parameter, such as baseline, safety, and PK/PD parameters; while standard error is provided for efficacy analysis to facilitate between-group comparisons. Geometric mean will be included for PK/PD variables. Categorical variables will be reported by the frequency and percentage of subjects within each outcome category. Two-sided 95% confidence intervals will be presented for key efficacy parameters and two-sided 90% confidence intervals for PK/PD parameters. All statistical tests will be performed at an α=0.05 level of significance, using two-sided tests, unless otherwise stated. Assessments as well as derived parameters will be presented in data listings for all subjects in the ITT/Safety Population.

9.3.2 Subject Enrollment and Disposition

The number of subjects in each study population as well as subject completion status and reasons for early discontinuation will be summarized.

9.3.3 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, and quality of life parameters.

9.4 Efficacy Analyses

Efficacy analyses will be based on the FAS population. Rules of handling missing data will be described in the Statistical Analysis Plan (SAP). Analyses based on observed data will be performed for sensitivity evaluation.

9.4.1 Primary Endpoint

The primary basis for assessment of efficacy will be the capacity of FG-3019 to reduce the rate of deterioration of FVC. The primary endpoint is the difference in annual FVC (% predicted) decline during treatment with FG-3019 compared with the annual decline prior to treatment with FG-3019. The posttreatment annual change in FVC (% predicted) will be compared to that prior to treatment using a mixed effect repeated measures model (MMRM), with adjustment of baseline FVC % predicted and use of corticosteroids. Effect of age (≤16 versus >16) and effect of disease characteristics at baseline, such as time since loss of ambulation, use of ventilation, spine surgery, will be evaluated and may be included in analysis models as appropriate. The difference in annual decline rate will be presented in two-sided 95% confidence interval. Two-sided test on whether the difference is significantly from zero will be reported.

The analysis of the primary endpoint will be based on the Full Analysis Set population. For subjects who drop out of the study early, their annual change in FVC % predicted will be estimated via the combination of available assessments and the MMRM model.

Change from baseline to one year and to two years in FVC (% predicted) will be estimated via the above mentioned MMRM model. If a substantial number of subjects drop out of the study before entering Year 2 treatment, change from baseline to 2 years will be estimated only for the subset of subjects who have provided Year 2 efficacy assessment.

9.4.2 Analyses of Other PFT Parameters

Changes from baseline to 1 year and 2 years in other PFT parameters will be estimated via the above MMRM model.

9.4.3 Analysis of PUL Parameters, Pinch and Grip Strength, Brooke Scale

Change from baseline to one year and to two years in hand/arm function and strength will be estimated using the MMRM model with dominant/non-dominant side as a fixed effect and baseline value and other relevant variables as covariates. In order to evaluate overall effect, composite scores may be explored. Two-sided 95% confidence intervals will be presented.

9.4.4 Analysis of LVEF, Cardiac Fibrosis, and Muscle Fat and Fibrosis

Changes from baseline in LVEF, cardiac fibrosis, and muscle fat and fibrosis will be summarized descriptively based on available data at Year 1 and at Year 2.

9.4.5 Analysis of PODCI Quality Outcome Data

Changes from baseline in modified PODCI scores of subjects will be summarized descriptively based on available data at Year 1 and at Year 2.

9.4.6 Examination of Subgroups

Comparisons in efficacy parameters between the following subgroups may be performed. Depending on enrollment in each subgroup, grouping may be adjusted to have relatively balanced sizes.

- Age ≤16 versus age >16
- Use of corticosteroids for at least 6 months during the first year of the study versus others
- Spine surgery: yes versus no
- Different genetic characteristics
- Above and below median in years of wheelchair bound
- Above versus below median of the baseline FVC (% predicted)
- Above versus below median of the hand and arm functional scale
- Above versus below median of the day 15 and the 6-month PK C_{min} levels
- Above versus below median of the baseline CTGF level

9.4.7 Pharmacokinetic Analyses

FG-3019 concentrations and derived PK parameters (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$) will be summarized using descriptive statistics. Pharmacokinetic analysis will be performed using commercial software such as WinNonlin.

Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters (1) in the overall population, (2) in subjects 12 to 16 years of age, and (3) in subjects older than 16 years. Comparison of PK parameters between the age groups will be performed. Trough values, measured at several time points during the course of the study, will be compared to determine steady state and accumulation.

9.4.8 Safety Analyses

Safety analyses will include summary of adverse events, prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs). In general, safety data will only be summarized descriptively and no inferential statistical procedures will be applied.

For data summarization, adverse events will be classified into standard terminology using a coding thesaurus (MedDRA), and reported by system organ class and preferred term. Treatment-emergent adverse events will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Deaths, SAEs, and AEs leading to study or treatment discontinuation, and infusion reactions will be listed or tabulated separately.

Clinically significant changes from baseline in vital signs, laboratory tests, and ECG will be identified. Shift tables will summarize changes in selected laboratory measures.

All safety analyses will be performed based on the Safety Population.

9.5 Interim and Administrative Analyses

In this open-label exploratory study, safety will be monitored on an ongoing basis and efficacy data will be evaluated periodically.

In addition to the above, a full review of efficacy and safety will be performed when PFT and other efficacy data up to and including Week 52 are available for all subjects. The study may be terminated if this review indicates that safety and efficacy endpoints will not be met after two years of treatment.

In addition, the DMC will review trends in PFTs and all other efficacy and safety data in accordance with the DMC charter.

9.6 Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will include unambiguous specifications for of all data analyses as well as documentation of changes in protocol-specified analysis plans. The SAP will describe additional study endpoints that are of interest.

10 DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the International Conference on Harmonisation (ICH) E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IVRS [or IWRS], clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The investigator must also permit the U.S. FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the investigator is notified of an inspection pertaining to this study by the U.S. FDA or other applicable regulatory authorities, the investigator must notify FibroGen immediately.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents

11.2 Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

11.3 Database Audit

A database audit will be conducted to ensure data quality and integrity.

12 ETHICS

12.1 Ethical Considerations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

12.2 Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

12.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent (ICF) and/or Assent Form from the subject or written Informed Consent Form signed by the subject's legally authorized representative, as applicable. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

12.4 Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

13 DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs/eCRFs and resolved queries.

13.2 Data Collection, Handling, and Verification

All required data will either be entered onto CRFs/eCRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with a full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion, ensuring that all data is verifiable with source documents.

14 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate document.

15 PUBLICATION POLICY

A detailed explanation of FibroGen's publication policy is described in the Clinical Trial Agreement.

16 REFERENCES

Au CG, Butler TL, Sherwood MC, Egan JR, North KN, Winlaw DS (2011) Increased connective tissue growth factor associated with cardiac fibrosis in the *mdx* mouse model of dystrophic cardiomyopathy. Int J Exp Pathol 92: (1):57-65

Bushby K, Finkel R, Birnkrant DJ, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 9: (1):77-93

Desguerre I, Mayer M, Leturcq F, Barbet JP, Gherardi RK, Christov C (2009) Endomysial fibrosis in Duchenne muscular dystrophy: a marker of poor outcome associated with macrophage alternative activation. J Neuropathol Exp Neurol 68: (7):762-773

Emery AE (1991) Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord 1: (1):19-29

Kharraz Y, Guerra J, Pessina P, Serrano AL, Munoz-Canoves P (2014) Understanding the process of fibrosis in Duchenne muscular dystrophy. Biomed Res Int **2014:**965631

Mayer OH, Finkel RS, Rummey C, et al. (2015) Characterization of pulmonary function in Duchenne Muscular Dystrophy. Pediatr Pulmonol 50: (5):487-494

McKim DA, Katz SL, Barrowman N, Ni A, LeBlanc C (2012) Lung volume recruitment slows pulmonary function decline in Duchenne muscular dystrophy. Archives of Physical Medicine and Rehabilitation 93: (7):1117-1122

Miller MR, Hankinson J, Brusasco V, et al. (2005) Standardisation of spirometry. Eur Respir J 26: (2):319-338

Morales MG, Cabello-Verrugio C, Santander C, Cabrera D, Goldschmeding R, Brandan E (2011) CTGF/CCN-2 over-expression can directly induce features of skeletal muscle dystrophy. J Pathol 225: (4):490-501

Morales MG, Gutierrez J, Cabello-Verrugio C, et al. (2013) Reducing CTGF/CCN2 slows down *mdx* muscle dystrophy and improves cell therapy. Hum Mol Genet 22: (24):4938-4951

Pessina P, Cabrera D, Morales MG, et al. (2014) Novel and optimized strategies for inducing fibrosis in vivo: Focus on Duchenne Muscular Dystrophy. Skelet Muscle 4:7

Phillips MF, Quinlivan RC, Edwards RH, Calverley PM (2001) Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med 164: (12):2191-2194

Schram G, Fournier A, Leduc H, et al. (2013) All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 61: (9):948-954

Sun G, Haginoya K, Wu Y, et al. (2008) Connective tissue growth factor is overexpressed in muscles of human muscular dystrophy. J Neurol Sci 267: (1-2):48-56

Tandon A, Villa CR, Hor KN, et al. (2015) Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. J Am Heart Assoc 4: (4):e001338

Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH (2001) Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. Arch Dis Child 84: (6):521-524

Vial C, Zuniga LM, Cabello-Verrugio C, Canon P, Fadic R, Brandan E (2008) Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. Journal of Cellular Physiology 215: (2):410-421

17 APPENDICES

Appendix 1 Schedule of Assessments: First Year of Treatment (Screening Period through Week 26)

Assessment[a]	Screening Period (4 Weeks)	Treatment Period (Weeks)													
		Day 0	2	4	6	8	10	12	14	16	18	20	22	24	26
Informed Consent & Assent	X														
Inclusion/ Exclusion	X														
Demographics	X														
Medical History	X														
Clinical laboratory assessments[b]	X[b]			X		X		X						X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X							X						X	
Electrocardiogram	X														
Physical Examination[e]	X	X						X						X	
Muscle function tests[f]	X	X						X						X	
Pulmonary function tests[g]	X	X						X						X	
Cardiac MRI	X														
Muscle MRI	X[i]														
Specialty labs[h]		X	X												X
FG-3019 infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire		X													X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1. Central labs are required at screening in addition to local labs that are required prior to the conduct of the MRIs.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected prior to start, within 15 minutes of infusion completion, and within 15 minutes of completing the observation period
d. Weight and height (estimated from ulna length) to be measured in screening and every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test
g. Pulmonary function tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details
i. Baseline muscle MRI may be conducted during the screening period or up to Week 4 dosing visit.

Appendix 2 Schedule of Assessments: First Year of Treatment (Weeks 28 through 52)

Assessment[a]	Treatment Period (Weeks)												
	28	30	32	34	36	38	40	42	44	46	48	50	52
Clinical laboratory assessments[b]					X						X		X[b]
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]					X						X		
Electrocardiogram													X
Physical Examination[e]					X						X		
Muscle function tests[f]					X						X		
Pulmonary function tests[g]					X						X		
Cardiac MRI													X
Muscle MRI													X
Specialty labs[h]													X
FG-3019 infusion	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire													X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1. At Week 52, only local labs are required prior to the conduct of the MRIs.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at screening and prior to start of infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured in screening and every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details

Appendix 3 Schedule of Assessments: Second Year of Treatment and Post-Treatment

	Treatment Period (Weeks)										Post-Treatment
Assessment[a]	**54, 56, 58**	**60**	**62, 64, 66, 68, 70**	**72**	**74, 76, 78, 80, 82**	**84**	**86, 88, 90, 92, 94**	**96**	**98, 100, 102**	**104/ EOT**	**Week 106 ±7 days or 4 Weeks After Last Dose for ET**
Clinical laboratory assessments[b]		X		X		X		X		X[b]	X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[c]		X		X		X		X		X	
Electrocardiogram										X	
Physical Examination[d]		X		X		X		X		X	X
Muscle function tests[e]		X		X		X		X		X	
Pulmonary function tests[f]		X		X		X		X		X	
Cardiac MRI										X	
Muscle MRI										X	
Specialty labs[g]					X				X	X	X
FG-3019 infusion	X	X	X	X	X	X	X	X	X		
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire										X	

Abbreviations: EOT= end of treatment; ET = Early Termination; MRI, magnetic resonance imaging, PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1. Central labs are required at Week 104/EOT in addition to local labs that are required prior to the conduct of the MRIs.Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected prior to start of infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period
c. Weight and height (estimated from ulna length) to be measured in screening and every 3 months thereafter. Do not measure weight at Week 104.
d. Physical exam to include assessment of subject's ventilation use.
e. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test
f. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
g. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details

Appendix 4 Pharmacokinetic and Pharmacodynamic Sampling Times

		Treatment Period										Post-Treatment
Sample	**Timepoint**	**Day 0**	**Day 2 ±1 day**	**Day 4 ±1 day**	**Day 7 ±1 day**	**Day 10 ±1 day**	**Week 2**	**Week 26**	**Week 52**	**Week 78**	**Week 102**	**Week 106 ±7 days or 4 Weeks After Last Dose for ET**
FG-3019 PK[a]	Before infusion	X					X	X	X	X	X	
	Within 1 hour after infusion	X							X		X	
	Time point sample (no infusion)		X	X	X	X						
HAHA[b]	Predose (when applicable)	X										X
CTGF[c]	Predose (when applicable)	X										X
Exploratory[d]	Predose (when applicable)	X							X		X	X

Abbreviations: CTGF = connective tissue growth factor; ET = early termination; HAHA = human anti-human antibody; PK = pharmacokinetic

a. Approximately 1-2 mL of blood will be collected for each measurement of FG-3019 PK.
b. Approximately 1 mL of blood will be collected for each measurement of HAHA.
c. Blood and urine samples will be collected. Approximately 1 mL of blood and 0.5 mL of urine will be collected for each measurement of CTGF.
d. Approximately 5 mL of blood will be collected for each exploratory sample.

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
PROTOCOL NUMBER:	FGCL-3019-079
PHASE:	2
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	126630
STUDY DRUG:	Pamrevlumab (FG-3019)
INDICATION:	Duchenne Muscular Dystrophy
FIBROGEN MEDICAL MONITOR	Name: [redacted] FibroGen, Inc. Title: [redacted] Telephone: [redacted] Mobile/Pager: [redacted] E-mail Address: [redacted]
ORIGINAL PROTOCOL:	16 June 2015
AMENDMENT 1.0	31 August 2015
AMENDMENT 2.0	06 May 2016
AMENDMENT 3.0	09 December 2016

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy

FGCL-3019-079

Original: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

Amendment 3.0: 09 December 2016

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen at the address provided below. Please retain the original for your study files.

Clinical Operations
FibroGen, Inc.
409 Illinois Street
San Francisco, California 94158 USA

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

Amendment 3.0: 09 December 2016

This protocol is approved by FibroGen.

[redacted]

09-Dec-2016

Date

FibroGen, Inc.

AMENDMENT 3.0: KEY CHANGES FROM AMENDMENT 2.0

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Key Change	Rationale	Sections Affected
Replacement FG-3019 with Pamrevlumab	Adoption of Pamrevlumab International Non-proprietary Name (INN) by United States Adopted Names Council (USAN)	Throughout entire document
Modified expected number of subjects enrolled from "approximately 22" to "up to 22"	Clarify expected number of subjects	Throughout entire document
Endpoint re-worded as follows for clarity: Change in annual forced vital capacity (FVC) (% predicted) decline during treatment of FG-3019 pamrevlumab compared with the estimated annual decline change prior to pamrevlumab FG-3019 treatment.	No change in meaning to this endpoint; endpoint re-worded for clarity.	Synopsis, 4.1.1 (Primary Endpoint); 9.4.1 (Primary Endpoint)
Decreased study duration from 104 Weeks to 52 Weeks with ability to continue for 26 additional weeks (78 Weeks total) for Subjects who achieve a ≤ 5% decline from baseline in FVC % predicted by week 52	Aligning with minimal anticipated treatment duration to detect efficacy signal in addition to allowing subjects who are benefiting from treatment to receive an additional 26 Weeks of treatment	Throughout entire document
Updated time on study to reflect Weeks vs Years (i.e. change from 1 Year to 52 Weeks)	Alignment with Appendix 1-4	Throughout entire document
Clarified that PK draws will only be completed in 12 subjects	Minimum number of complete samples needed to assess PK	Synopsis, Section 4.1.3 (Exploratory, Pharmacokinetic and Pharmacodynamic Outcome Measures)
Removal of Interim Analysis at Week 52	No longer applicable as study duration has been decreased from 104 Week to 52 Weeks of treatment	Synopsis, Section 4.2 (Trial Objections), Section 9.5 (Administrative Analysis)
Deletion Wheelchair dependency <5 years from Inclusion Criteria #3	FVC requirement defines the targeted patient population; wheelchair time restriction overly restrictive	Synopsis, Section 5.1 (Inclusion Criteria)
Inclusion Criteria #8 revised to allow only enrollment of subjects with an FVC percent predicted between 40 and 90, inclusive	FVC percent predicted criteria greater than 50 may not be clinically feasible in target population	Synopsis, Section 5.1 (Inclusion Criteria)

Key Change	Rationale	Sections Affected
Deletion of "estimated annual decline of FVC (% predicted) of ≥ 5% based upon at least 2 PFTs done in the previous 18 months, in addition to the screening FVC" from Inclusion Criteria #9. Criteria changed to "At least one historical FVC % predicted value within 18 months of baseline".	Inclusion criteria requiring ≥ 5% based upon at least 2 PFTs done in the previous 18 months overly restrictive	Synopsis, Section 5.1 (Inclusion Criteria)
Modification of Inclusion Criteria #11 from "Stable regimen of heart failure cardiac medications (e.g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) for at least 3 months prior to screening" to "Subjects currently receiving heart failure cardiac medications (e.g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening"	Clarify that this is only intended for subject currently receiving heart failure cardiac medications	Synopsis, Section 5.1 (Inclusion Criteria)
Modification of Inclusion Criteria #15, adequate hematological function bullet point b: Hemoglobin value updates from >10 g/dL to >12 g/dL	Align with normal hematologic function for targeted population	Synopsis, Section 5.1 (Inclusion Criteria)
Modification of Inclusion Criteria #15, adequate hematological function bullet point c: Absolute Neutrophil Count value updates from >1000/mcL to 1500/µL	Align with normal hematologic function for targeted population	Synopsis, Section 5.1 (Inclusion Criteria)
Modification of Inclusion Criteria #16, adequate hepatic function bullet point b: Gamma glutamyl transferase (GGT) value updates from ≤2x upper limit of normal (ULN) to ≤3x upper limit of normal (ULN)	Align with normal hepatic function for targeted population	Synopsis, Section 5.1 (Inclusion Criteria)
Modification of Exclusion Criteria #2 to update timeframe of any prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of treatment and follow-up would be completed, or could impair the assessment of study result from 2 years to 78 weeks	Align with longest time a subject may be on study	Synopsis, Section 5.2 (Exclusion Criteria)
Modification of Exclusion Criteria #3 to update timeframe of anticipated spine surgery from 2 years to 78 weeks	Align with longest timeframe a subject may be on study	Synopsis, Section 5.2 (Exclusion Criteria)

Key Change	Rationale	Sections Affected
Modification of Exclusion Criteria #10 to clarify that the use of another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days or 5 half-lives of the product whichever is longer prior to first screening visit with the exception of deflazacort is exclusionary. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.	Patients may have been on newly approved product for DMD and could be confounding.	Synopsis, Section 5.2 (Exclusion Criteria)
Deletion of Exclusion Criteria #11	Redundant with Exclusion Criteria #10. Use of deflazacort integrated into Exclusion #10	Synopsis, Section 5.2 (Exclusion Criteria)
Clarification that any approved product for DMD (e.g. eteplirsen) during study treatment is prohibited	In order to clearly assess impact of Pamrevlumab in study population	Synopsis, Section 4.4 (Concomitant Medications, Procedures and Nondrug Therapies)
Update to Pamrevlumab dosing schedule for Phase 1 and 2 studies investigating the pharmacokinetics (PK)	Update to align with Investigator Brochure v16	Section 2.3.2 (Pharmacokinetics)
Update to pharmacokinetics (PK) 1/2 life of Pamrevlumab in trial in pancreatic cancer	Update to align with Investigator Brochure v16	Section 2.3.2 (Pharmacokinetics)
Clarification that the DMC's responsibility includes review of safety data *and may include* available pharmacokinetics data and pulmonary function tests	In order to clearly define additional data this may be available to the DMC to complete their safety review.	Section 4.6 (Data Monitoring Committee), Section 9.5 (Administrative Analysis)
Clarification that subjects who weigh more than 117 kg will receive a maximum allowed dose of 4.1 g.	Clearly define the maximum allowable dose of pamrevlumab	Section 6.1.4 (Administration)
Clarification that conduct of pulmonary function tests should be delayed until the subject can reliably perform the assessment if they are unable to perform adequately due to illness (i.e. sinusitis, etc.).	Exclude tests being performed at times when subject performance may be sub-optimal and negatively impact results/interpretation	Section 7.1.1 (Screening Period)
Deletion of Section 11.3 (database audit)	Section is meant for paper CRFS studies not Electronic Data Capture studies	Section 11.3
Updates to Schedule of Assessments	Alignment with shortened duration of study	Appendices 1-4

PROTOCOL SYNOPSIS

Study Title:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
Protocol Number:	FGCL-3019-079, Amendment 3.0
Investigational Product:	Pamrevlumab (FG-3019) (Recombinant fully human IgG_1 kappa monoclonal antibody to connective tissue growth factor)
Study Phase:	Phase 2
Target Population:	Non-ambulatory subjects with Duchenne muscular dystrophy (DMD)
Number of Subjects Planned:	Up to 22
Study Centers Planned:	Approximately 10 centers

OBJECTIVES

Primary Objective

To estimate pamrevlumab s efficacy in non-ambulatory subjects with DMD

Secondary Objectives

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

ENDPOINTS/ASSESSMENTS

Efficacy

Primary Endpoint

- Change in annual forced vital capacity (FVC) (% predicted) during treatment of pamrevlumab compared with the estimated annual change prior to pamrevlumab treatment.

Secondary Endpoints

- Change from baseline to 52 weeks in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow

- Change in LVEF from baseline to Week 52
- Change from baseline to Week 52 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 52 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 52 in cardiac fibrosis score assessed by magnetic resonance imaging (MRI)
- Change from baseline to Week 52 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

Exploratory, Pharmacokinetics, Pharmacodynamics

In the first 12 subjects to have complete PK/PD samples:

- Pharmacokinetic (PK) profile of pamrevlumab (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$)
  - In the overall population
  - In subjects 12 to 16 years of age, inclusive
  - In subjects older than 16 years
  - Comparison of PK profiles across age groups
- Plasma and urine connective tissue growth factor (CTGF)
- Creatine kinase (CK)
- Circulating biomarkers

Safety

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

STUDY DESIGN

This study will be an open-label, single arm study of up to 22 subjects. Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for up to 52 weeks (Initial Phase). Subjects who achieve a ≤ 5% decline from baseline in FVC % predicted by Week 52 will qualify for extended treatment. The extended treatment phase of the study will include an additional 26 weeks of treatment for a total of 78 weeks of treatment at the same dose/schedule. For those subjects who meet the above criteria, prior FibroGen medical monitor approval is required for continuation into the extended treatment phase.

All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow).

STUDY PROCEDURES

Details regarding study procedures are provided as follows:

Appendix 1: Screening Period through Week 26 of Initial Phase

Appendix 2: Week 28 through End of Treatment Initial Phase

Appendix 3: Extended Treatment Phase

Appendix 4: Pharmacokinetic and Pharmacodynamic Sampling Times

MAIN SELECTION CRITERIA

Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. At least one historical FVC % predicted value within 18 months of baseline
10. Left ventricular ejection fraction >45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Subjects currently receiving heart failure cardiac medications (e.g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation.
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /µL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤3x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after last dose of study drug.

Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 78 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 78 weeks
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

TREATMENTS

Pamrevlumab Dose, and Mode of Administration

Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for 52 weeks (Initial Phase). Subjects who achieve a ≤ 5% decline from baseline in FVC % predicted by Week 52 will qualify for extended treatment. The extended treatment phase of the study will include an additional 26 weeks of treatment for a total of 78 weeks of treatment at the same dose/schedule. For those subjects who meet the above criteria, prior FibroGen medical monitor approval is required for continuation into the extended treatment phase. The dose of pamrevlumab (35 mg/kg) for each infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken every 3 months thereafter.

Reference Therapy: Not applicable

Concomitant Medications/Therapies: Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy. Investigational agents, and those that receive marketing authorization, or approved product for DMD (e.g. eteplirsen) during this trial are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care

is allowed. Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

STATISTIC METHODS

This study will enroll up to 22 subjects. A sample size of 22 subjects will provide 84% power to detect an absolute difference of 3.5% in FVC % predicted, using a two-sided, one-sample paired t-test to compare the annual change posttreatment with that prior to treatment at significance level 0.05. This calculation is based on assumption of standard deviation of 5% and assumption of two dropouts without any efficacy assessments at study completion.

The primary basis for assessment of efficacy will be the capacity of pamrevlumab to reduce the rate of deterioration of FVC. The primary endpoint is the change in annual FVC (% predicted) decline during treatment with pamrevlumab compared with the annual decline prior to treatment with pamrevlumab. The posttreatment annual change in FVC (% predicted) will be compared to that prior to treatment using a mixed effect repeated measures model (MMRM), with adjustment of baseline FVC% predicted and use of corticosteroid. Effect of age (≤16 versus >16) and effect of disease characteristics at baseline, such as time since loss of ambulation, use of ventilation, spine surgery, type of genetic mutation, will be evaluated and may be included in analysis models as appropriate. The difference in annual decline rate will be presented in two-sided 95% confidence interval. Two-sided test on whether the difference is significantly different from zero will be reported.

The analysis of the primary endpoint will be based on the Full Analysis Set population. For subjects who drop out of the study early, their annual change in FVC% predicted will be estimated via the combination of available assessments and the MMRM model.

Change from baseline to 52 Weeks in FVC (% predicted) will be estimated via the above mentioned MMRM model.

Summary statistics for observed values, change from baseline, and percent change from baseline will be reported for all secondary endpoints. For those secondary outcomes where historical data is available, the effect of pamrevlumab may be investigated further by performing repeated measures analyses.

Pamrevlumab concentrations and derived PK parameters will be tabulated and summarized using descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters. Attainment of steady-state will be investigated.

Safety analyses will include summary of adverse events (including treatment emergent AEs, treatment emergent serious AEs, deaths, and infusion-associated AEs), prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs), and physical exams.

TABLE OF CONTENTS

LIST OF APPENDICES

2 BACKGROUND

2.1 Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G_1 (IgG) kappa monoclonal antibody to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role. These diseases include liver fibrosis due to hepatitis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne muscular dystrophy (DMD). Pamrevlumab (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. Pamrevlumab contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2 Duchenne Muscle Dystrophy

Duchenne muscular dystrophy (DMD) is usually inherited in an X-linked recessive fashion, but it can occur as a result of spontaneous mutation in boys from families without a known history of the condition. On the basis of some 40 studies including several million male births, incidence at birth of Duchenne muscular dystrophy is around 1:3300, and its prevalence in the population (in terms of the total male population) is around 1:16500 (Emery, 1991).

DMD is a result of mutations (mainly deletions) in the dystrophin gene (DMD; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration with loss of independent ambulation by the age of 13 years (Bushby, 2010).

In skeletal muscles of DMD patients constant myofiber breakdown results in persistent activation of myofibroblasts and altered production of extracellular matrix (ECM) resulting in extensive fibrosis. Muscle fibrosis is the only myo-pathologic parameter that significantly correlated with poor motor outcome as assessed by quadriceps muscle strength, manual muscle testing of upper and lower limbs, and age at ambulation loss (Desguerre, 2009).

Patients with DMD are generally wheelchair bound before they develop significant respiratory muscle weakness. Respiratory complications are the primary cause of morbidity and mortality in DMD as progressive respiratory muscle weakness leads to hypoventilation and/or recurrent atelectasis and pneumonia, secondary to decreased cough effectiveness (McKim, 2012).

After age 10 to 14, patients gradually begin to lose respiratory muscle function based on pulmonary function tests (PFTs) such as forced vital capacity (FVC). The median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001, Tangsrud, 2001).

Because of improvements in respiratory care, cardiac dysfunction is now a leading cause of morbidity and mortality in DMD patients (Schram, 2013). Progressive myocardial fibrosis, as detected by late gadolinium enhancement (LGE), is strongly correlated with the left ventricular ejection fraction (LVEF) decline in Duchenne muscular dystrophy patients. Longer steroid treatment duration is associated with a lower age-related increase in myocardial fibrosis burden (Tandon, 2015).

2.2.1 Relevance of Connective Tissue Growth Factor (CTGF) in DMD

Connective tissue growth factor (CTGF) is a nonstructural regulatory protein present in the extracellular matrix that has an important role in fibrosis. Skeletal muscle from DMD patients, dystrophic dogs, and mdx mice all show elevated levels of CTGF (Sun, 2008).

CTGF can reproduce or amplify the effects of TGFβ on fibrosis by inducing collagen type 1, α5 integrin, and fibronectin much more potently than TGFβ in fibroblasts (Kharraz, 2014).

Comparison of mdx mice with normal or genetically depleted levels of CTGF revealed that exercised mice with reduced CTGF developed less fibrosis and exhibited better muscle strength than mice with normal levels of CTGF (Morales, 2013). In culture, both myoblasts and myotubes were shown to express and secrete CTGF to the medium, and respond to the growth factor by increasing the extracellular matrix constituents, partially inhibiting myoblasts differentiation and inducing myoblasts dedifferentiation (Vial, 2008).

In DMD, the role of CTGF might extend well beyond replacement fibrosis secondary to loss of muscle fibers, since its overexpression in skeletal muscle could by itself induce a dystrophic phenotype (Morales, 2013).

A major feature of the hearts of DMD patients is cardiac fibrosis. Cardiac fibrosis is associated with increased CTGF expression in the *mdx* mouse heart. CTGF may be a key mediator of early and persistent fibrosis in dystrophic cardiomyopathy (Au, 2011).

CTGF is critically involved in several chronic fibro-degenerative diseases. Pamrevlumab treatment has been shown to positively the affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.

2.3 A Summary of Relevant Findings from Nonclinical Studies and from Clinical Trials

Please refer to the most recent version of pamrevlumab Investigator's Brochure.

2.3.1 Nonclinical Studies

In DMD, the genetic loss of the cytoskeletal protein dystrophin results in muscle damage that, leads to progressive replacement of muscle with fibrotic and fat tissue. This progressive muscle damage can be recapitulated in the DMD mouse model (*mdx*), and accelerated by muscle usage (Pessina, 2014).

As was observed with genetic depletion of CTGF, pharmacologic inhibition of active CTGF in *mdx* mice by treatment with pamrevlumab resulted in reduced fibrosis and skeletal muscle damage, as well as improved preservation of skeletal muscle strength in isolated muscles. The pamrevlumab treated *mdx* mice were also subjected to a test of exercise endurance, in which they showed better performance than *mdx* mice injected with control IgG (Morales, 2013).

Pamrevlumab treatment of *mdx* mice was associated with decreased skeletal muscle damage and fibrosis, decreased collagen III and fibronectin expression, decreased plasma creatine kinase (CK) (Morales, 2013), and increased isometric force of skeletal muscle (Morales, 2011).

2.3.2 Pharmacokinetics

Key findings are summarized below from Phase 1 and 2 studies investigating the pharmacokinetics (PK) of pamrevlumab in subjects with diabetic kidney disease, idiopathic pulmonary fibrosis, liver fibrosis and pancreatic cancer:

- Pamrevlumab was administered over the dose range of 3 to 45 mg/kg every 2 weeks, every 3 weeks, and 17.5 to 22.5 mg/kg weekly.
- Pamrevlumab exposure (e.g., mean/median C_{max} and C_{min}, area under the curve [AUC]) generally increased with increasing dose.
- For single dose studies, for doses > 10 mg/kg the $t_{1/2}$ did not appear to increase with increasing pamrevlumab doses, based on available data with estimated mean $t_{1/2}$ values of approximately 1 week.
- For multiple dose studies, the mean $t_{1/2}$ following multiple doses (3 to 10 mg/kg) also increased from 102 to 135 hours.
    - The estimated $t_{1/2}$ values for doses > 10 mg/kg did not appear to increase markedly with dose, based on available data (limited time points).

2.3.3 Safety

Key findings are summarized below from the Phase 1 and 2 studies involving more than 400 adults with diabetic kidney disease, idiopathic pulmonary fibrosis, and liver fibrosis due to hepatitis B or pancreatic cancer:

- Overall, pamrevlumab was well tolerated across the range of doses noted above, and there were no dose-limiting toxicities.
- Treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity and transient in duration.
- Infusion-related reactions have been mild-to-moderate and did not recur following re-administration of pamrevlumab
- TEAEs were considered typical of the subjects' underlying medical condition(s) and, in the placebo-controlled studies, were equally distributed between placebo and pamrevlumab treatment groups.
- No apparent pattern to TEAEs that occurred within 24 hours after infusions was observed.
- No apparent pattern for treatment-emergent serious adverse events (TESAEs) was observed during clinical testing.

2.3.4 Efficacy

Key efficacy findings are summarized below from the Phase 1 and 2 studies of CTGF inhibition by pamrevlumab in indications other than DMD.

2.3.4.1 Pancreatic Cancer

Biweekly doses of up to and including 45 mg/kg and weekly doses of 17.5 and 22.5 mg/kg were administered to subjects with previously untreated locally advanced or metastatic pancreatic adenocarcinoma. Increased exposure to pamrevlumab was associated with increased survival. There appears to be a relationship between survival and trough blood levels of pamrevlumab (C_{min}). Notably C_{min} >150 mcg/mL after the first dose of pamrevlumab (Day 15) was associated with significantly increased progression free survival and overall survival.

A maximal effect in survival benefit was achieved at dose levels of 25 to 45 mg/kg/2 weeks.

2.3.4.2 Idiopathic Pulmonary Fibrosis (IPF)

In subjects with IPF who completed 45 weeks of dosing with 15 or 30 mg/kg pamrevlumab, approximately 40% of subjects had stable or improved lung fibrosis by quantitative high resolution CT imaging compared to baseline values with approximately 30% having improved pulmonary fibrosis.

Overall, subjects with stable or improved lung fibrosis also had stable or improved FVC (% predicted).

2.4 Risks and Benefits

Pamrevlumab has been generally well tolerated with most adverse events being typical of those expected for subjects with the underlying disease conditions.

Infusion-related reactions have been rarely observed in some subjects treated with pamrevlumab. Across studies in other indications, infusion-related reactions have been mild-to-moderate did not result in discontinuation of treatment with pamrevlumab, and did not result in the use of prophylaxis for subsequent infusions.

The favorable experience with pamrevlumab to date does not exclude the possibility of more severe infusion reactions occurring in future subjects.

This is the first clinical study of pamrevlumab in DMD. There are currently no confirmed benefits to subjects with DMD treated with pamrevlumab. However, a potential benefit of treatment with pamrevlumab is indicated in preclinical models of DMD and previous clinical studies of pamrevlumab in other indications where CTGF is also associated with disease progression.

Dose regimens equal to or exceeding 35 mg/kg have been implemented in other indications in adult subjects. The objective of these studies was to inhibit bioactive CTGF, which is associated with disease progression in a number of indications. Please refer to the Investigator's Brochure for a comprehensive summary of efficacy, safety, and exposure data.

The current study will explore the clinical relevance of CTGF inhibition, as indicated in preclinical models, in DMD patients.

2.5 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Periods

Pamrevlumab is administered as an IV infusion at a dose of 35 mg/kg every two weeks for one year (Day 0 to Week 52). Subjects who achieve a ≤ 5% decline from baseline in FVC % predicted by Week 52 may continue on extended treatment, at the same dose/schedule, for an additional 26 weeks (total of 78 weeks of treatment) with prior FibroGen medical monitor approval. The dose, frequency and route of administration correspond with dose regimens that were well tolerated and possibly associated with efficacy in clinical studies in adults with IPF and pancreatic cancer. In both of these indications pamrevlumab was administered at doses that included the targeted dose regimen for the current study (35 mg/kg bodyweight) and greater (45 mg/kg bodyweight). These doses were not associated with dose limiting toxicity.

The overall objective of all of these studies, including the current study, is to provide a dose associated with clinically relevant CTGF blockade to impede progression of serious disease states. Body weight-related dosing and utilization of a dose no greater than the maximal dose used in adults are expected to ensure that systemic exposure in the targeted pediatric population will not exceed the systemic exposure achieved in adults.

PK assessments will be done during the course of the study and facilitate ongoing monitoring of exposure to pamrevlumab during the course of the study.

The planned treatment duration is no longer than total treatment periods achieved in previous studies with pamrevlumab.

The duration of treatment of the current study is also similar to the duration of other studies in DMD and is expected to provide sufficient basis to evaluate potential benefit in the targeted pediatric population with DMD.

2.6 Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents. Detailed information regarding study conduct is found in Sections 10, 11, 12, and 13.

2.7 Population to be Studied

Non-ambulatory adolescents and adults with DMD will be enrolled in this trial.
A detailed inclusion/exclusion list is provided in Section 5.

3 OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is to estimate pamrevlumab's efficacy in non-ambulatory subjects with DMD.

3.2 Secondary Objectives

The following are the secondary objectives of this trial:

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

4 STUDY DESIGN

4.1 Endpoints and Assessments

4.1.1 Primary Endpoint

The primary endpoint is the change from baseline to Week 52 in in annual forced vital capacity (FVC) (% predicted) during treatment of pamrevlumab compared with the estimated annual change prior to pamrevlumab treatment.

4.1.2 Secondary Endpoints

The following are the secondary endpoints:

- Change from baseline to Week 52 in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow
- Change in LVEF from baseline to Week 52
- Change from baseline to Week 52 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 52 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 52 in cardiac fibrosis score assessed by MRI
- Change from baseline to Week 52 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

4.1.3 Exploratory, Pharmacokinetic and Pharmacodynamic Outcome Measures

Exploratory outcome measures for this trial are:

In the first 12 subjects to have complete PK/PD samples:

- Pharmacokinetic (PK) profile of pamrevlumab (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$)
    - In the overall population
    - In subjects 12 to 16 years of age, inclusive
    - In subjects older than 16 years
    - Comparison of PK profiles across age groups
- Plasma and urine CTGF
- Creatine kinase (CK)
- Circulating biomarkers

4.1.4 Safety Assessments

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

4.2 Trial Overview

This study will be an open-label, single arm study of up to 22 subjects. Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for up to 52 weeks (Initial Phase). Subjects who achieve a ≤ 5% decline in FVC % predicted by Week 52 may continue on extended treatment, at the same dose/schedule, for an additional 26 weeks (total of 78 weeks of treatment) with prior FibroGen medical monitor approval. All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow) on a continuous basis.

Upon completion of treatment or premature discontinuation from the trial, subjects will be asked to return to the investigative site to complete final safety and efficacy assessments.

4.3 Study Treatment

4.3.1 Dose and Schedule

Each subject will receive pamrevlumab (35 mg/kg) intravenously every 2 weeks (q2w). See Section 6 for detailed information on study drug formulation, storage, and administration.

4.3.2 Rationale for Dose and Schedule

The pamrevlumab dose is based on results of a study in adult subjects with pancreatic cancer. In that study (Section 2.3.4.1), minimum pamrevlumab blood levels (C_{min}) ≥150 mcg/mL were associated with increased median survival and 1 year survival compared to subjects with C_{min} <150 mcg/mL. Given the apparent threshold effect for increased benefit when minimal pamrevlumab exposure is ≥150 mcg/mL and based on PK analysis using these data, the planned dose of 35 mg/kg administered every 2 weeks is projected to achieve this minimum exposure in the targeted DMD study population.

4.4 Concomitant Medications, Procedures and Nondrug Therapies

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy.

Investigational agents, and those that receive marketing authorization during this trial, or approved product for DMD (e.g. eteplirsen) are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

Concomitant medications (any prescription and/or over-the-counter [OTC] preparation) and procedures or nondrug therapies (e.g., physical therapy or acupuncture) used by a subject while participating in this clinical trial must be recorded from the Screening Visit through the End-of-Study Visit.

Questions regarding potential impact of concomitant medications on evaluability of subjects enrolled in the study should be addressed to the attention of the FibroGen Medical Monitor or designee.

4.4.1 Contraception

Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy of a partner must be reported (Section 8.3.6).

4.5 Safety Plan

An ongoing safety review is facilitated by the unblinded nature of the study. FibroGen will review safety data and will communicate the results of these reviews to investigators by email or teleconference on a regular basis. In addition, FibroGen will review safety experience with investigators during teleconferences that will be held at least quarterly and include the conclusions of the Data Monitoring Committee's (DMC) latest data review.

FibroGen will notify investigators immediately if a new safety risk is identified.

4.6 Data Monitoring Committee

A DMC will be utilized and will be composed of external and internal (FibroGen) experts. Composition and responsibilities of the DMC are defined in a separate DMC charter.

DMC responsibilities include review of safety data, and may include available pharmacokinetic data, and pulmonary function tests.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. At least one historical FVC % predicted value within 18 months of baseline
10. Left ventricular ejection fraction >45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Subjects currently receiving heart failure cardiac medications (e.g. angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /μL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤3 x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after the last dose of study drug

5.2 Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 78 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 78 weeks
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

5.3 Subject Withdrawal

Subjects may withdraw from the study at any time.

The investigator will remove a subject from study treatment for the following reasons:

- Adverse events, which in the opinion of the Principal Investigator and/or FibroGen preclude further study drug dosing
- Nonadherence to protocol-defined procedures, in particular missing of 3 or more sequential study drug infusions
- Not available for safety assessments

Subjects who discontinue the study early should be strongly encouraged to complete the evaluations described in Section 7.1.3.

5.4 Replacement of Subjects

Subjects may be replaced in this study if a subject's participation is not terminated due to safety or tolerability issues and is replaced prior to completion of targeted recruitment of up to 22 subjects into the study. Replacement decisions will be made between the sponsor and investigator on a case-by-case basis.

5.5 Study Termination

This trial can be terminated by the sponsor at any time for any reason.

6 STUDY DRUG/TREATMENT SUPPLY

6.1 FibroGen Investigational Product

Pamrevlumab is a fully human IgG_1 kappa monoclonal antibody that binds to CTGF.

6.1.1 Formulation

Pamrevlumab is supplied in single-use glass vials containing 10 mL of a sterile, preservative-free solution. The solution is composed of 10 mg/mL pamrevlumab, 1.60 mg/mL l-histidine, 3.08 mg/mL l-histidine HCl, 8.01 mg/mL sodium chloride and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0.

6.1.2 Storage

Vials of pamrevlumab must be stored refrigerated (2°C to 8°C), in a temperature-controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation.

6.1.3 Preparation of Dose for Administration

The dose of pamrevlumab (35 mg/kg) for each infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken every 3 months thereafter. Pamrevlumab may be administered undiluted or, for convenience of infusion, may be diluted with 0.9% Sodium Chloride Injection according to the Dose Preparation Instructions in the Study Reference Investigational Product (IP) Manual.

Pamrevlumab will be administered as soon as possible after release from the site's pharmacy and within 24 hours of preparation. Pamrevlumab will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

6.1.4 Administration

Study Drug	Dose	Route	Infusion Rate	Schedule
Pamrevlumab	35 mg/kg	IV	Not to exceed 150 cc/hour	Every 2 weeks
DO NOT ADMINISTER PAMREVLUMAB AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.				

Subjects who weigh more than 117 kg will receive the maximum allowed dose of 4.1 g. For this study, the overall rate of infusion for the prepared study drug should not exceed 150 cc/hour. Adjustments may be made to further slow the rate of infusion (infusing less than 150 cc/hour) in accordance with the investigator's clinical judgement. Subjects should be carefully monitored for reaction during the first infusion with a physician available as needed. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation. The IV access should remain in place and be maintained per site procedures until the end of this posttreatment observation period.

If a subject has an infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences an infusion reaction and continues pamrevlumab dosing, a physician must be immediately available during subsequent infusions and observation periods until the subject does not have any infusion reaction for three sequential infusions.

Premedication, such as antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are not normally administered before infusions of pamrevlumab. Premedication may be used for subjects who experience infusion reactions at the discretion of the investigator after discussion with the Medical Monitor.

Pamrevlumab will be administered in a hospital or ambulatory setting with adequate facilities for managing medical emergencies for at least three infusions to confirm the subject does not have an infusion reaction. The study site must have trained staff and medications for the treatment of acute reactions, including anaphylaxis, immediately available. There is no specific treatment for a pamrevlumab overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

FibroGen may consider the use of properly trained home health care staff to administer the pamrevlumab infusions in the future and corresponding study assessments during the conduct of the study, consistent with institutional regulations and policies.

7 ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

7.1 Study Procedures by Visit

All study procedures and assessments will be performed in accordance with the Schedule of Assessments presented in the Appendices.

For all potential subjects, screening procedures required to determine subject eligibility will be performed within 28 days prior to Day 0 (first infusion of pamrevlumab). Potential subjects may be re-screened if initial screening procedures lie outside the 28-day screening period prior to planned study entry.

Subject's eligibility for this study will be reviewed and approved by Sponsor's medical monitor prior to subject enrollment.

The following assessments are relevant to the assessment of efficacy: pulmonary function tests (FVC, mean inspiratory flow (MIF), peak expiratory flow), Brooke Upper Extremity Rating Scale, Performance of the Upper Limb, pinch strength, grip strength, cardiac MRI, and muscle MRI. Refer to the Study Reference Manual for details.

Approved windows for performing study assessments are defined in the following sections.

7.1.1 Screening Period (no earlier than Day -28)

Assessments to be conducted during the screening period are presented in Appendix 1.

Screening assessments may be completed over several visits during the screening period. It is recommended that the less invasive screening assessments be performed first upon completion of the signed Informed Consent and/or Assent Form [ICF] (demographics, medical history, blood draws, electrocardiogram [ECG], vital signs (includes body weight and height), physical exam, pulmonary function tests (PFTs), and then followed by the more rigorous screening assessments (i.e., muscle function tests, cardiac MRI).

A cardiac MRI performed within 3 months prior to Day 0 (start of dosing) is acceptable to confirm eligibility based on the LVEF study entry criterion and as baseline cardiac MRI. If an historic MRI is not available, a cardiac MRI must be performed during the Screening Period.

An upper arm muscle MRI is not required to determine subject eligibility at screening, but may be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Muscle and pulmonary function tests (PFTs) will be performed during the screening period. Muscle function and PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.

If the subject cannot perform adequately due to illness (e.g. sinusitis, etc.) then the PFTs should be delayed until the subject can reliably perform the assessment within the 28-day screening window.

In addition, an exploratory blood sample will be drawn for analysis of circulating biomarkers of fibrosis and specific muscle miRNAs (dystromirs) prior to first pamrevlumab infusion.

7.1.2 Dosing Period

The initial dosing period begins on the first day of dosing with study treatment (Day 0) and continues through Week 52. Subjects who achieve a ≤ 5% decline from baseline FVC % predicted by Week 52 may continue on extended treatment, at the same dose/schedule, for additional 26 weeks (total of 78 weeks of treatment) with prior FibroGen medical monitor approval. Subjects will receive study drug every 2 weeks.

The visit window for all dosing visits is ±2 days. Visits should be scheduled based on the previous visit, not the baseline visit.

Assessments and procedures to be performed during the dosing period are presented in Appendices 1-4.

Muscle or pulmonary function tests that cannot be performed or produce inadequate results according to test procedures during a specified visit should be performed by the next scheduled dosing visit.

Both cardiac and muscle MRIs may be performed within ±2 weeks of the specified visit.

Blood samples will be drawn for pharmacokinetic analysis according to the schedule in Appendix 4. Blood draws to be collected on non-dosing days may be collected within ±1 day as outlined in Appendix 4.

7.1.3 End of Treatment

Assessments and procedures to be conducted after the last dose of study drug are presented in Appendix 2-Appendix 3.

For subjects who do not go on to extended treatment, the end of treatment cardiac and muscle MRIs may be performed any time from Week 54/EOT to Week 56.

For subjects who continue on study for an additional 26 weeks (Extended Treatment), the end of treatment cardiac and muscle MRIs may be performed any time from Week 80/EOT to Week 82.

7.1.4 Early Withdrawal from Treatment

Subjects who prematurely discontinue the study should be strongly encouraged to complete the final efficacy evaluations scheduled for Weeks 54 (Initial Treatment) or 80 (Extended Treatment) as applicable, and the safety follow-up evaluations scheduled for Week 56 (Initial Treatment) or 82 (Extended Treatment) (4 weeks following the last dose).

7.1.5 End of Treatment and Safety Follow-Up Period

For subjects who complete 52 weeks and do not receive extended treatment, final study evaluations will be performed at Week 54/EOT.

For subjects who complete 78 weeks, final study evaluations will be performed at Week 80/EOT.

For all subjects, the final safety assessments should be completed 4 weeks (±7 days) after the last dose of pamrevlumab.

7.1.6 Missed Visits

Every attempt must be made to complete all study visits as outlined in the Schedules of Assessments. Missed infusions will not be replaced. If a subject misses a scheduled efficacy assessment, the assessment should be performed as soon after the missed visit as feasible and within the windows specified above.

7.1.7 Unscheduled Visits

Unscheduled Visit assessments may be required at the discretion of the investigator.

7.2 Assessments

Please refer to the Schedules of Assessments (Appendix 1-Appendix 4) for the scope and timing of assessments. Please refer to the Laboratory Manual for details regarding laboratory sample collection and processing; and the Study Reference Manual for details regarding the conduct of functional tests and MRIs.

7.2.1 Pulmonary Function Tests

The following pulmonary function tests (PFTs) will be performed to assess changes in lung function: forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow rate (PEF; PEFR), forced expiratory volume in 1 second (FEV1), and peak cough flow (Mayer, 2015, Miller, 2005).

7.2.2 Muscle Strength and Functional Measurements

The following assessments will be performed to assess changes in upper extremity strength and function: Brooke Upper Extremity Rating Scale (Brooke Scale), Performance of the Upper Limb (PUL), Grip Test, and Pinch Strength Test.

7.2.3 Cardiac MRI

For subjects who do not meet the criteria for extended treatment Cardiac MRIs, will be performed during screening and at Week 54/EOT to assess changes in left ventricular ejection fraction (LVEF) and presence of late gadolinium enhancement (LGE), a marker for myocardial fibrosis.

For subjects who meet the criteria for extended treatment Cardiac MRIs, will be performed during screening, Week 54 and at Week 80/EOT to assess changes in left ventricular ejection fraction (LVEF) and presence of late gadolinium enhancement (LGE), a marker for myocardial fibrosis.

7.2.4 Muscle MRI

An upper arm muscle MRI at screening, will be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

For subjects who do not go on to extended treatment upper arm (bicep) muscle MRIs will be performed at Week 54/EOT to assess changes in degree of fatty replacement of select muscle groups by T2 relaxation time mapping.

For subjects who go on to extended treatment, upper arm (bicep) muscle MRIs will be performed at Week 54 and at Week 80/EOT.

7.2.5 Quality of Life Questionnaire

Pediatrics Outcomes Data Collection Instrument (PODCI) Quality Outcome Questionnaire will be performed to assess if treatment with pamrevlumab improves quality of life.

7.2.6 Vital Signs and Physical Examinations

A physical examination will be performed at screening and baseline (Day 0), approximately every 12 weeks and at end of treatment and post-treatment safety follow-up. Complete physical exams will be performed at screening, Week 54, and Week 80/EOT (for those subjects continuing onto extended treatment). Other examinations may be disease-specific or problem-oriented examinations.

Vital signs (pulse, respiration, sitting blood pressure, and temperature) will be collected at screening and prior to start of each infusion, within 15 minutes of the end of each infusion, and within 15 minutes of the completion of the post-infusion observation period.

7.2.7 Laboratory Assessments

All laboratory tests of blood and/or urine specimens will be performed at a central laboratory or FibroGen, as appropriate. A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local clinical laboratories will be used to assess and facilitate the management of adverse events and to provide usual standard of care (including blood draws required prior to MRIs). Local clinical laboratory data will not be collected in the study database except for hematocrit values provided with imaging data.

7.2.7.1 Safety Assessments

Blood samples will be 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.

Safety labs will be drawn at the site's local lab prior to MRIs to ensure there is no contraindication to MRI. Hematocrit should be included in the local lab draw as these results are required to assess fibrosis and will be provided to the central imaging vendor along with the MRI scans. Details are included in the Imaging Manual.

7.2.7.2 Pharmacokinetics

Plasma concentrations of pamrevlumab will be determined on Day 0 pre-dose and within 1 hour post infusion, then on Days 2, 4, 7, 10, and 14. The Day 14 sample should be on the same day of, but prior to the start of the next infusion of study drug.

Day 2, 4, 7, and 10 PK assessments represent target days following the first dose; however, actual sample collection time of up to ±1 day of the target time is acceptable as

long as the actual time of dosing and actual time of each sample collection are recorded accurately.

At Weeks 26 and 52, trough pamrevlumab levels (C_{min}) will be determined prior to study drug infusion.

PK samples will also be drawn within 60 minutes of infusion completion at Week 52.

7.2.7.3 Plasma and Urine CTGF

Plasma and urine samples will be analyzed for CTGF concentrations from samples taken as described in Appendix 4.

7.2.7.4 HAHA

Blood samples will be drawn for analysis of human anti-human antibody (HAHA) according to the schedule in Appendix 4.

7.2.7.5 Biomarkers

Blood samples will be drawn for analysis of biomarkers. The exact biomarkers will be based on current scientific knowledge regarding CTGF, pamrevlumab and DMD at the time the tests are performed. No genetic testing will be performed.

8 ASSESSMENT OF SAFETY

8.1 Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 1-Appendix 3. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the Study Drug.

8.2 Definitions

8.2.1 Definition of an Adverse Event (AE)

For the purpose of this study, an AE is any untoward medical occurrence that occurred in the protocol-specified AE reporting period, and which does not necessarily have a causal relationship with the study drug. An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.3.1).

8.2.2 Definition of a Serious Adverse Event (SAE)

A **serious adverse event** is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.2.3 Definition of an Infusion Reaction

Infusion reactions are immunologic reactions to an infused protein, and are different from events resulting from the process of infusing the protein (e.g., infusion site bruise) and are different from adverse events due to the infused protein's intended or unintended pharmacologic effects.

8.2.3.1 Acute Infusion Reaction

An acute infusion reaction is one that meets both of the following criteria:

1. Occurs during or within 1 hour after infusion; and
2. Clinical manifestations consistent with:
    - IgE-mediated and non-IgE mediated hypersensitivity reactions, including but not limited to urticaria, skin rashes, angioedema, laryngeal edema, bronchospasm, gastrointestinal symptoms and hypotension; or
    - Cytokine release syndrome, including but not limited to fever, respiratory symptoms without the presence of wheezing, tremors, chills, flushing, pruritus, changes in blood pressure, dyspnea, chest discomfort, back pain, nausea, vomiting, diarrhea, and skin rashes.

8.2.3.2 Delayed Infusion Reaction

A delayed infusion reaction is one that meets both of the following criteria:

1. Occurs ≥1 hour after the infusion
2. Clinical manifestations as described above.

8.2.3.3 Reporting Possible and Confirmed Infusion Reactions

Both acute and delayed infusion reactions will be captured as AEs and also be reported to the medical monitor within 24 hours. See Study Reference Manual for additional details.

8.2.4 Special Situations

Certain safety events, called 'Special Situations' that occur in association with the study drug(s) include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving the medicinal product (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

Special Situations will be reported to the sponsor or designated vendor within 24 hours on a Medication Error report form. See Study Reference Manual for details.

8.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 4 weeks after the last dose of study drug, except for pregnancy reporting (Section 8.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5).

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever is possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff.

New indications for medications started during the AE reporting period (i.e., after informed consent is obtained until 4 weeks after the last dose of study drug) will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the Investigator to meet the specified criteria.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

8.3.3 Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 4.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild**: Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; ; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death:** Fatal AE.

8.3.4 Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- **Related:**
    - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re-occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.

- **Not Related:**
    - The event represents a pre-existing underlying disease that has not worsened on study
    - The event has the same characteristics of a known side-effect associated with a co-medication
    - The event is an anticipated medical condition of anticipated severity for the study population
    - The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5 Reporting Serious Adverse Events on the SAE Report Form

An SAE must be reported to the Sponsor and/or its designated safety management vendor within 24 hours of becoming aware of the SAE.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

The contact information for SAE reporting is as follows:

U.S. Toll-Free Fax Number: [redacted]

Email: [redacted]

8.3.5.1 Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2 Deaths

The investigator will report the fatal or life-threatening event immediately to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to 4 weeks after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. Additionally, the site must complete the appropriate CRF page.

8.3.6 Pregnancies: Reporting and Follow-up of Subjects

The outcome of all pregnancies should be followed up and documented as described. Consent must be obtained from male subject's partner to collect information related to the pregnancy and outcome (and will be handled on a case-by-case basis with IRB/IEC approval). A Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

8.3.7 Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all laboratory results throughout the study in a timely manner, and determine whether any abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

8.3.8 Risk Management/Monitoring Programs

No specific risk management programs will be implemented.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

This study tests the hypothesis of whether pamrevlumab can attenuate the annual decline in FVC in non-ambulatory DMD patients. Without treatment, the median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001). The goal of pamrevlumab treatment is to reduce the annual loss to 4.5%. An enrollment of up to 22 subjects is planned in order to detect a reduction of 3.5% in annual FVC decline with at least 80% power, using a two sided one-sample paired t-test at a significance level of 0.05. This power calculation is based on a standard deviation of 5% and that two subjects will dropout without any efficacy assessments. A mixed-effect repeated measures model will be used in the analysis so that assessments from early dropouts will be utilized.

9.2 Analysis Populations

9.2.1 Safety Population

The Safety Population will consist of all subjects who have received any dose of pamrevlumab. This population is also defined as the intent-to-treat (ITT) population.

9.2.2 Full Analysis Set Population

The Full Analysis Set Population (FAS) will consist of all subjects in the Safety Population who have at least one evaluable post-baseline FVC assessment.

9.3 Statistical Analysis

9.3.1 General Considerations

Descriptive summaries will be provided for all study parameters including baseline characteristics, safety, efficacy, pharmacokinetic and pharmacodynamic parameters. Continuous variables will be reported using number of subjects, mean, standard deviation or standard error, median, minimum, and maximum. In general, standard deviation is provided to describe the distribution of a parameter, such as baseline, safety, and PK/PD parameters; while standard error is provided for efficacy analysis to facilitate between-group comparisons. Geometric mean will be included for PK/PD variables. Categorical variables will be reported by the frequency and percentage of subjects within each outcome category. Two-sided 95% confidence intervals will be presented for key efficacy parameters and two-sided 90% confidence intervals for PK/PD parameters. All statistical tests will be performed at an α=0.05 level of significance, using two-sided tests, unless otherwise stated. Assessments as well as derived parameters will be presented in data listings for all subjects in the ITT/Safety Population.

9.3.2 Subject Enrollment and Disposition

The number of subjects in each study population as well as subject completion status and reasons for early discontinuation will be summarized.

9.3.3 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, and quality of life parameters.

9.4 Efficacy Analyses

Efficacy analyses will be based on the FAS population. Rules of handling missing data will be described in the Statistical Analysis Plan (SAP). Analyses based on observed data will be performed for sensitivity evaluation.

9.4.1 Primary Endpoint

The primary basis for assessment of efficacy will be the capacity of pamrevlumab to reduce the rate of deterioration of FVC. The primary endpoint is the change in annual FVC (% predicted) during treatment with pamrevlumab compared with the annual change prior to treatment with pamrevlumab. The posttreatment annual change in FVC (% predicted) will be compared to that prior to treatment using a mixed effect repeated measures model (MMRM), with adjustment of baseline FVC % predicted and use of corticosteroids. Effect of age (≤16 versus >16) and effect of disease characteristics at baseline, such as time since loss of ambulation, use of ventilation, spine surgery, will be evaluated and may be included in analysis models as appropriate. The difference in annual change will be presented in two-sided 95% confidence interval. Two-sided test on whether the difference is significantly from zero will be reported.

The analysis of the primary endpoint will be based on the Full Analysis Set population. For subjects who drop out of the study early, their annual change in FVC % predicted will be estimated via the combination of available assessments and the MMRM model.

Change from baseline to Week 52 in FVC (% predicted) will be estimated via the above mentioned MMRM model.

9.4.2 Analyses of Other PFT Parameters

Changes from baseline to Week 52 in other PFT parameters will be estimated via the above MMRM model.

9.4.3 Analysis of PUL Parameters, Pinch and Grip Strength, Brooke Scale

Change from baseline to Week 52 in hand/arm function and strength will be estimated using the MMRM model with dominant/non-dominant side as a fixed effect and baseline value and other relevant variables as covariates. In order to evaluate overall effect, composite scores may be explored. Two-sided 95% confidence intervals will be presented.

9.4.4 Analysis of LVEF, Cardiac Fibrosis, and Muscle Fat and Fibrosis

Changes from baseline in LVEF, cardiac fibrosis, and muscle fat and fibrosis will be summarized descriptively based on available data at Week 52.

9.4.5 Analysis of PODCI Quality Outcome Data

Changes from baseline in modified PODCI scores of subjects will be summarized descriptively based on available data at each assessment time point.

9.4.6 Examination of Subgroups

Comparisons in efficacy parameters between the following subgroups may be performed. Depending on enrollment in each subgroup, grouping may be adjusted to have relatively balanced sizes.

- Age ≤16 versus age >16
- Use of corticosteroids for at least 6 months during the first year of the study versus others
- Spine surgery: yes versus no
- Different genetic characteristics
- Above and below median in years of wheelchair bound
- Above versus below median of the baseline FVC (% predicted)
- Above versus below median of the hand and arm functional scale
- Above versus below median of the day 15 and the 6-month PK C_{min} levels
- Above versus below median of the baseline CTGF level

9.4.7 Pharmacokinetic Analyses

Pamrevlumab concentrations and derived PK parameters (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$) will be summarized using descriptive statistics. Pharmacokinetic analysis will be performed using commercial software such as WinNonlin.

Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters (1) in the overall population, (2) in subjects 12 to 16 years of age, and (3) in subjects older than 16 years. Comparison of PK parameters between the age groups will be performed. Trough values, measured at several time points during the course of the study, will be compared to determine steady state and accumulation.

9.4.8 Safety Analyses

Safety analyses will include summary of adverse events, prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs). In general, safety data will only be summarized descriptively and no inferential statistical procedures will be applied.

For data summarization, adverse events will be classified into standard terminology using a coding thesaurus (MedDRA), and reported by system organ class and preferred term. Treatment-emergent adverse events will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Deaths, SAEs, and AEs leading to study or treatment discontinuation, and infusion reactions will be listed or tabulated separately.

Clinically significant changes from baseline in vital signs, laboratory tests, and ECG will be identified. Shift tables will summarize changes in selected laboratory measures.

All safety analyses will be performed based on the Safety Population.

9.5 Administrative Analyses

In this open-label exploratory study, safety will be monitored on an ongoing basis and efficacy data will be evaluated periodically.

The DMC will review all safety data, which may include available pharmacokinetic data, and pulmonary function tests.

9.6 Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will include unambiguous specifications for of all data analyses as well as documentation of changes in protocol-specified analysis plans. The SAP will describe additional study endpoints that are of interest.

10 DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the International Conference on Harmonisation (ICH) E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IVRS [or IWRS], clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The investigator must also permit the U.S. FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the investigator is notified of an inspection pertaining to this study by the U.S. FDA or other applicable regulatory authorities, the investigator must notify FibroGen immediately.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents

11.2 Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

12 ETHICS

12.1 Ethical Considerations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

12.2 Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

12.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent (ICF) and/or Assent Form from the subject or written Informed Consent Form signed by the subject's legally authorized representative, as applicable. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

12.4 Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

13 DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs/eCRFs and resolved queries.

13.2 Data Collection, Handling, and Verification

All required data will either be entered onto CRFs/eCRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with a full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion, ensuring that all data is verifiable with source documents.

14 FINANCING AND INSURANCE

Financing and insurance are addressed in a separate document.

15 PUBLICATION POLICY

A detailed explanation of FibroGen's publication policy is described in the Clinical Trial Agreement.

16 REFERENCES

Au CG, Butler TL, Sherwood MC, Egan JR, North KN, Winlaw DS (2011) Increased connective tissue growth factor associated with cardiac fibrosis in the *mdx* mouse model of dystrophic cardiomyopathy. Int J Exp Pathol 92: (1):57-65

Bushby K, Finkel R, Birnkrant DJ, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 9: (1):77-93

Desguerre I, Mayer M, Leturcq F, Barbet JP, Gherardi RK, Christov C (2009) Endomysial fibrosis in Duchenne muscular dystrophy: a marker of poor outcome associated with macrophage alternative activation. J Neuropathol Exp Neurol 68: (7):762-773

Emery AE (1991) Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord 1: (1):19-29

Kharraz Y, Guerra J, Pessina P, Serrano AL, Munoz-Canoves P (2014) Understanding the process of fibrosis in Duchenne muscular dystrophy. Biomed Res Int **2014:**965631

Mayer OH, Finkel RS, Rummey C, et al. (2015) Characterization of pulmonary function in Duchenne Muscular Dystrophy. Pediatr Pulmonol 50: (5):487-494

McKim DA, Katz SL, Barrowman N, Ni A, LeBlanc C (2012) Lung volume recruitment slows pulmonary function decline in Duchenne muscular dystrophy. Archives of Physical Medicine and Rehabilitation 93: (7):1117-1122

Miller MR, Hankinson J, Brusasco V, et al. (2005) Standardisation of spirometry. Eur Respir J 26: (2):319-338

Morales MG, Cabello-Verrugio C, Santander C, Cabrera D, Goldschmeding R, Brandan E (2011) CTGF/CCN-2 over-expression can directly induce features of skeletal muscle dystrophy. J Pathol 225: (4):490-501

Morales MG, Gutierrez J, Cabello-Verrugio C, et al. (2013) Reducing CTGF/CCN2 slows down *mdx* muscle dystrophy and improves cell therapy. Hum Mol Genet 22: (24):4938-4951

Pessina P, Cabrera D, Morales MG, et al. (2014) Novel and optimized strategies for inducing fibrosis in vivo: Focus on Duchenne Muscular Dystrophy. Skelet Muscle 4:7

Phillips MF, Quinlivan RC, Edwards RH, Calverley PM (2001) Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med 164: (12):2191-2194

Schram G, Fournier A, Leduc H, et al. (2013) All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 61: (9):948-954

Sun G, Haginoya K, Wu Y, et al. (2008) Connective tissue growth factor is overexpressed in muscles of human muscular dystrophy. J Neurol Sci 267: (1-2):48-56

Tandon A, Villa CR, Hor KN, et al. (2015) Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. J Am Heart Assoc 4: (4):e001338

Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH (2001) Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. Arch Dis Child 84: (6):521-524

Vial C, Zuniga LM, Cabello-Verrugio C, Canon P, Fadic R, Brandan E (2008) Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. Journal of Cellular Physiology 215: (2):410-421

17 APPENDICES

Appendix 1 Schedule of Assessments: Screening Period through Week 26 of Initial Phase

Assessment[a]	Screening Period (4 Weeks)	Treatment Period (Weeks)													
		Day 0	2	4	6	8	10	12	14	16	18	20	22	24	26
Informed Consent & Assent	X														
Inclusion/ Exclusion	X														
Demographics	X														
Medical History	X														
Clinical laboratory assessments[b]	X[b]			X		X		X						X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X							X						X	
Electrocardiogram	X														
Physical Examination[e]	X	X						X						X	
Muscle function tests[f]	X	X						X						X	
Pulmonary function tests[g]	X	X						X						X	
Cardiac MRI	X														
Muscle MRI	X[i]														
Specialty labs[h]		X	X												X
Pamrevlumab infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire		X													X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at screening in addition to local labs that are required prior to the conduct of the MRIs.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected prior to start, within 15 minutes of infusion completion, and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured in screening and every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at screening. Other exams may be disease specific or problem oriented.
f. Muscle function tests (MFT): Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test. MFTs will be performed during the screening period. MFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
g. Pulmonary function tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow. PFTs will be performed during the screening period. PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Baseline muscle MRI may be conducted during the screening period or up to Week 4 dosing visit.

Appendix 2 Schedule of Assessments: Week 28 through End of Treatment Initial Phase

Assessment[a]	Treatment Period (Weeks)														Safety Follow-up
	28	30	32	34	36	38	40	42	44	46	48	50	52	54/ EOT	Week 56 ±7 days or 4 Weeks After Last Dose for ET
Clinical laboratory assessments[b]					X						X		X[b]		X[b]
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]					X						X			X[d]	
Electrocardiogram													X		
Physical Examination[e]					X						X			X	X
Muscle function tests[f]					X									X	
Pulmonary function tests[g]					X								X		
Cardiac MRI														X	
Muscle MRI														X	
Specialty labs[h]													X		X
Pamrevlumab infusion[i]	X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire													X		

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at Week 56/Safety Follow-Up in addition to local labs that are required prior to the conduct of the MRIs.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at screening and prior to start of infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured in screening and approximately every 3 months thereafter. Do not measure weight at Week 54/EOT.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 80/EOT. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. For subjects continuing on to the Extended Treatment Phase Pamrevlumab will be infused at Week 54

Appendix 3 Schedule of Assessments: Extended Treatment Phase

Assessment[a]	Treatment Period (Weeks)								Safety Follow-up
	56, 58	60	62	64	66, 68, 70	72	74, 76, 78	80/ EOT	Week 82 ±7 days or 4 Weeks After Last Dose for ET
Clinical laboratory assessments[b]		X				X			X
Vital Signs[c]	X	X	**X**	**X**	X	X	X	X	X
Weight/Height[d]		X				X		X	
Electrocardiogram								X	
Physical Examination[e]		X				X		X	X
Muscle function tests[f]		X				X		X	
Pulmonary function tests[g]				X				X	
Cardiac MRI								X	
Muscle MRI								X	
Specialty labs[h]									X
Pamrevlumab infusion	X	X	X	X	X	X	X		
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire								X	

Abbreviations: EOT= end of treatment; ET = Early Termination; MRI, magnetic resonance imaging, PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows for assessments and dosing
b. Safety labs: See Section 7.2.7.1. Central labs are required at Week 82/Safety Follow-Up in addition to local labs that are required prior to the conduct of the MRIs.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected prior to start of infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period
d. Weight and height (estimated from ulna length) to be measured in screening and approximately every 3 months thereafter. It is not necessary to measure weight at Week 80/EOT.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 80/EOT. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details

Appendix 4 Pharmacokinetic and Pharmacodynamic Sampling Times

		Treatment Period								Safety Follow-up
Sample	**Timepoint**	**Day 0**	**Day 2 ±1 day**	**Day 4 ±1 day**	**Day 7 ±1 day**	**Day 10 ±1 day**	**Week 2**	**Week 26**	**Week 52**	**Week 56 ±7 days or Week 82 ±7 days or 4 Weeks After Last Dose for ET**
Pamrevlumab PK[a]	Before infusion	X					X	X	X	
	Within 1 hour after infusion	X							X	
	Time point sample (no infusion)		X	X	X	X				
HAHA[b]	Predose (when applicable)	X								X
CTGF[c]	Predose (when applicable)	X								X
Exploratory[d]	Predose (when applicable)	X							X	

Abbreviations: CTGF = connective tissue growth factor; ET = early termination; HAHA = human anti-human antibody; PK = pharmacokinetic

a. Approximately 1-2 mL of blood will be collected for each measurement of pamrevlumab PK.
b. Approximately 1 mL of blood will be collected for each measurement of HAHA.
c. Blood and urine samples will be collected. Approximately 1 mL of blood and 0.5 mL of urine will be collected for each measurement of CTGF.
d. Approximately 5 mL of blood will be collected for each exploratory sample.

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
PROTOCOL NUMBER:	FGCL-3019-079
PHASE:	2
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	126630
STUDY DRUG:	Pamrevlumab (FG-3019)
INDICATION:	Duchenne Muscular Dystrophy
FIBROGEN MEDICAL MONITOR	[redacted] FibroGen, Inc. [redacted] Telephone: [redacted] Mobile: [redacted] E-mail Address: [redacted]
ORIGINAL PROTOCOL:	16 June 2015
AMENDMENT 1.0	31 August 2015
AMENDMENT 2.0	06 May 2016
AMENDMENT 3.0	09 December 2016
AMENDMENT 4.0	10 July 2017

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy

FGCL-3019-079

Original: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

Amendment 3.0: 09 December 2016

Amendment 4.0: 10 July 2017

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen's designee. Please retain the original for your study files.

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

Amendment 3.0: 09 December 2016

Amendment 4.0: 10 July 2017

This protocol is approved by FibroGen.

[redacted]

7/12/2017

Date

FibroGen, Inc.

AMENDMENT 4.0: KEY CHANGES FROM AMENDMENT 3.0

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Key Change	Rationale	Sections Affected
Sample size changed to reflect that study may enroll up to 32 subjects dependent on outcome of interim analysis	Anticipated that 22 subjects may not be large enough sample size to determine defined treatment effect	Synopsis, Protocol Sections 4.2, 5.4 and 9
Extended treatment duration from 52 weeks plus extension, to 104 weeks; removed extension, and added interim analysis	Anticipated that 1 year may not be sufficient treatment duration to see treatment effect	Synopsis, Protocol Sections 2.5, 4.1.2, 4.2, 7.1.2-7.1.5, 7.2.3-7.2.6, 9, Schedule of Assessments
Changed primary endpoint to annual change in percent predicted annual forced vital capacity (FVC) during treatment with pamrevlumab	Endpoint modified to reflect natural history of DMD in wheelchair bound patients	Synopsis, Protocol Sections 4.1.1 and 9
Corrected to reflect that DMC members are all external	Reflects actual DMC membership	Protocol Section 4.6
Changed exclusion criteria 2 and 3 to reflect increased treatment duration	Based on extended treatment duration	Synopsis, Protocol Section 5.2
Corrected subject withdrawal language to reflect that PIs may choose to with draw subjects early.	Prior language stated incorrectly that they ‘will’ withdraw instead of ‘may’ withdraw.	Protocol Section 5.3
Added that new pamrevlumab vial size and/or formulation information would be provided in Pharmacy Manual updates and site training	Extension of study treatment period suggests that new vial sizes and formulations may be introduced during course of study.	Protocol Section 6.1.1
Amended language to reflect that only the first infusion is based on the Screening weight.	Prior language stated that each infusion would be based on Screening weight but later infusions are adjusted based on weight measured every 3 months.	Synopsis, Protocol Section 6.1.3
Updated to reflect that infusion reactions are considered an identified risk of pamrevlumab administration and deleted that they did not recur with readministration.	Aligned with Investigator Brochure Version 16	Protocol Section 2.3.3, 2.4
Minor typos and formatting corrections	Formatting, typos	Throughout

PROTOCOL SYNOPSIS

Study Title:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
Protocol Number:	FGCL-3019-079, Amendment 4.0
Investigational Product:	Pamrevlumab (FG-3019) (Recombinant fully human IgG_1 kappa monoclonal antibody to connective tissue growth factor)
Study Phase:	Phase 2
Target Population:	Non-ambulatory subjects with Duchenne muscular dystrophy (DMD)
Number of Subjects Planned:	Approximately 22 subjects will be enrolled; interim analysis may increase sample size to approximately 32
Study Centers Planned:	Approximately 10 centers

OBJECTIVES

Primary Objective

To estimate pamrevlumab's efficacy in non-ambulatory subjects with DMD

Secondary Objectives

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

ENDPOINTS/ASSESSMENTS

Efficacy

Primary Endpoint

- Annual change in percent predicted annual forced vital capacity (FVC) during treatment with pamrevlumab.

Secondary Endpoints

- Change from baseline to 104 weeks in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow

- Change in LVEF from baseline to Week 104
- Change from baseline to Week 104 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 104 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 104 in cardiac fibrosis score assessed by magnetic resonance imaging (MRI)
- Change from baseline to Week 104 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

Exploratory, Pharmacokinetics, Pharmacodynamics

In the first 12 subjects to have complete PK/PD samples:

- Pharmacokinetic (PK) profile of pamrevlumab (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$)
  - In the overall population
  - In subjects 12 to 16 years of age, inclusive
  - In subjects older than 16 years
  - Comparison of PK profiles across age groups
- Plasma and urine connective tissue growth factor (CTGF)
- Creatine kinase (CK)
- Circulating biomarkers

Safety

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

STUDY DESIGN

This study is an open-label, single arm study which will initially enroll approximately 22 subjects. Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for up to 104 weeks. An interim analysis will be conducted after at least 12 subjects have completed 52 weeks of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

All subjects will be closely monitored for safety (including trends of pulmonary

function tests: FVC, mean inspiratory flow, and peak expiratory flow).

STUDY PROCEDURES

Details regarding study procedures are provided as follows:
Appendix 1: Screening Period through Week 26

Appendix 2: Week 28 through Week 58

Appendix 3: Week 60 through Week 106/EOS

Appendix 4: Specialty Lab Schedule

MAIN SELECTION CRITERIA

Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. At least one historical FVC % predicted value within 18 months of baseline
10. Left ventricular ejection fraction >45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Subjects currently receiving heart failure cardiac medications (e.g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation.
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations

14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /μL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤3x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after last dose of study drug.

Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 104 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 104 weeks
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

TREATMENTS

Pamrevlumab Dose, and Mode of Administration

Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for 104 weeks. The dose of pamrevlumab (35 mg/kg) for the first infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken every 3 months thereafter.

Concomitant Medications/Therapies:

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy. Investigational agents, and those that receive marketing authorization, or approved product for DMD (e.g. eteplirsen) during this trial are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care

is allowed. Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

STATISTICAL METHODS

A total of 22 subjects is planned to achieve 80% power to test the null hypothesis of change in percent predicted FVC of -5% against the alternative hypothesis, assuming a mean change of -2% and standard deviation of 5%, based on a 2-sided one sample t-test at 0.05 significance level.

The primary efficacy endpoint will be met if the annual change in percent predicted FVC is above -5% after 104 weeks of treatment with pamrevlumab (lower bound of the 2-sided 95% confidence interval is above -5%).

An interim analysis will be conducted for potential sample size readjustment; the sample size may be expanded to a total of approximately 32 subjects as needed.

The primary efficacy endpoint is the annual change in percent predicted FVC during treatment with pamrevlumab. The mean annual change in percent predicted FVC and the corresponding 2-sided 95% confidence interval will be presented.

Final analysis of the primary and secondary endpoints will be described in the statistical analysis plan. Details of the interim analysis will be described in an interim analysis plan.

Pamrevlumab concentrations and derived PK parameters will be tabulated and summarized using descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters. Attainment of steady-state will be

investigated.

Safety analyses will include summary of adverse events (including treatment emergent AEs, treatment emergent serious AEs, deaths, and infusion-associated AEs), prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs), and physical exams.

TABLE OF CONTENTS

LIST OF APPENDICES

2 BACKGROUND

2.1 Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G_1 (IgG) kappa monoclonal antibody to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role. These diseases include liver fibrosis due to hepatitis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne muscular dystrophy (DMD). Pamrevlumab (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. Pamrevlumab contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2 Duchenne Muscle Dystrophy

Duchenne muscular dystrophy (DMD) is usually inherited in an X-linked recessive fashion, but it can occur as a result of spontaneous mutation in boys from families without a known history of the condition. On the basis of some 40 studies including several million male births, incidence at birth of Duchenne muscular dystrophy is around 1:3300, and its prevalence in the population (in terms of the total male population) is around 1:16500 (Emery, 1991).

DMD is a result of mutations (mainly deletions) in the dystrophin gene (DMD; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration with loss of independent ambulation by the age of 13 years (Bushby, 2010).

In skeletal muscles of DMD patients constant myofiber breakdown results in persistent activation of myofibroblasts and altered production of extracellular matrix (ECM) resulting in extensive fibrosis. Muscle fibrosis is the only myo-pathologic parameter that significantly correlated with poor motor outcome as assessed by quadriceps muscle strength, manual muscle testing of upper and lower limbs, and age at ambulation loss (Desguerre, 2009).

Patients with DMD are generally wheelchair bound before they develop significant respiratory muscle weakness. Respiratory complications are the primary cause of morbidity and mortality in DMD as progressive respiratory muscle weakness leads to hypoventilation and/or recurrent atelectasis and pneumonia, secondary to decreased cough effectiveness (McKim, 2012).

After age 10 to 14, patients gradually begin to lose respiratory muscle function based on pulmonary function tests (PFTs) such as forced vital capacity (FVC). The median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001, Tangsrud, 2001).

Because of improvements in respiratory care, cardiac dysfunction is now a leading cause of morbidity and mortality in DMD patients (Schram, 2013). Progressive myocardial fibrosis, as detected by late gadolinium enhancement (LGE), is strongly correlated with the left ventricular ejection fraction (LVEF) decline in Duchenne muscular dystrophy patients. Longer steroid treatment duration is associated with a lower age-related increase in myocardial fibrosis burden (Tandon, 2015).

2.2.1 Relevance of Connective Tissue Growth Factor (CTGF) in DMD

Connective tissue growth factor (CTGF) is a nonstructural regulatory protein present in the extracellular matrix that has an important role in fibrosis. Skeletal muscle from DMD patients, dystrophic dogs, and mdx mice all show elevated levels of CTGF (Sun, 2008).

CTGF can reproduce or amplify the effects of TGFβ on fibrosis by inducing collagen type 1, α5 integrin, and fibronectin much more potently than TGFβ in fibroblasts (Kharraz, 2014).

Comparison of mdx mice with normal or genetically depleted levels of CTGF revealed that exercised mice with reduced CTGF developed less fibrosis and exhibited better muscle strength than mice with normal levels of CTGF (Morales, 2013). In culture, both myoblasts and myotubes were shown to express and secrete CTGF to the medium, and respond to the growth factor by increasing the extracellular matrix constituents, partially inhibiting myoblasts differentiation and inducing myoblasts dedifferentiation (Vial, 2008).

In DMD, the role of CTGF might extend well beyond replacement fibrosis secondary to loss of muscle fibers, since its overexpression in skeletal muscle could by itself induce a dystrophic phenotype (Morales, 2013).

A major feature of the hearts of DMD patients is cardiac fibrosis. Cardiac fibrosis is associated with increased CTGF expression in the *mdx* mouse heart. CTGF may be a key mediator of early and persistent fibrosis in dystrophic cardiomyopathy (Au, 2011).

CTGF is critically involved in several chronic fibro-degenerative diseases. Pamrevlumab treatment has been shown to positively the affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.

2.3 Summary of Relevant Findings from Nonclinical and Clinical Trials

Please refer to the most recent version of pamrevlumab Investigator's Brochure.

2.3.1 Nonclinical Studies

In DMD, the genetic loss of the cytoskeletal protein dystrophin results in muscle damage that, leads to progressive replacement of muscle with fibrotic and fat tissue. This progressive muscle damage can be recapitulated in the DMD mouse model (*mdx*), and accelerated by muscle usage (Pessina, 2014).

As was observed with genetic depletion of CTGF, pharmacologic inhibition of active CTGF in *mdx* mice by treatment with pamrevlumab resulted in reduced fibrosis and skeletal muscle damage, as well as improved preservation of skeletal muscle strength in isolated muscles. The pamrevlumab treated *mdx* mice were also subjected to a test of exercise endurance, in which they showed better performance than *mdx* mice injected with control IgG (Morales, 2013).

Pamrevlumab treatment of *mdx* mice was associated with decreased skeletal muscle damage and fibrosis, decreased collagen III and fibronectin expression, decreased plasma creatine kinase (CK) (Morales, 2013), and increased isometric force of skeletal muscle (Morales, 2011).

2.3.2 Pharmacokinetics

Key findings are summarized below from Phase 1 and 2 studies investigating the pharmacokinetics (PK) of pamrevlumab in subjects with diabetic kidney disease, idiopathic pulmonary fibrosis, liver fibrosis and pancreatic cancer:

- Pamrevlumab was administered over the dose range of 3 to 45 mg/kg every 2 weeks, every 3 weeks, and 17.5 to 22.5 mg/kg weekly.
- Pamrevlumab exposure (e.g., mean/median C_{max} and C_{min}, area under the curve [AUC]) generally increased with increasing dose.
- For single dose studies, for doses > 10 mg/kg the $t_{1/2}$ did not appear to increase with increasing pamrevlumab doses, based on available data with estimated mean $t_{1/2}$ values of approximately 1 week.
- For multiple dose studies, the mean $t_{1/2}$ following multiple doses (3 to 10 mg/kg) also increased from 102 to 135 hours.
    - The estimated $t_{1/2}$ values for doses > 10 mg/kg did not appear to increase markedly with dose, based on available data (limited time points).

2.3.3 Safety

Key findings are summarized below from the Phase 1 and 2 studies involving more than 400 adults with diabetic kidney disease, idiopathic pulmonary fibrosis, and liver fibrosis due to hepatitis B or pancreatic cancer:

- Overall, pamrevlumab was well tolerated across the range of doses noted above, and there were no dose-limiting toxicities.
- Treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity and transient in duration.
- Infusion-related reactions have been mild-to-moderate and are considered an identified risk of pamrevlumab administration.
- TEAEs were considered typical of the subjects' underlying medical condition(s) and, in the placebo-controlled studies, were equally distributed between placebo and pamrevlumab treatment groups.
- No apparent pattern to TEAEs that occurred within 24 hours after infusions was observed.
- No apparent pattern for treatment-emergent serious adverse events (TESAEs) was observed during clinical testing.

2.3.4 Efficacy

Key efficacy findings are summarized below from the Phase 1 and 2 studies of CTGF inhibition by pamrevlumab in indications other than DMD.

2.3.4.1 Pancreatic Cancer

Biweekly doses of up to and including 45 mg/kg and weekly doses of 17.5 and

22.5 mg/kg were administered to subjects with previously untreated locally advanced or metastatic pancreatic adenocarcinoma. Increased exposure to pamrevlumab was associated with increased survival. There appears to be a relationship between survival and trough blood levels of pamrevlumab (C_{min}). Notably C_{min} >150 mcg/mL after the first dose of pamrevlumab (Day 15) was associated with significantly increased progression free survival and overall survival.

A maximal effect in survival benefit was achieved at dose levels of 25 to 45 mg/kg/2 weeks.

2.3.4.2 Idiopathic Pulmonary Fibrosis (IPF)

In subjects with IPF who completed 45 weeks of dosing with 15 or 30 mg/kg pamrevlumab, approximately 40% of subjects had stable or improved lung fibrosis by quantitative high resolution CT imaging compared to baseline values with approximately 30% having improved pulmonary fibrosis.

Overall, subjects with stable or improved lung fibrosis also had stable or improved FVC (% predicted).

2.4 Risks and Benefits

Pamrevlumab has been generally well tolerated with most adverse events being typical of those expected for subjects with the underlying disease conditions.

Infusion-related reactions have been observed in some subjects treated with pamrevlumab. Across studies in other indications, infusion-related reactions have been mild-to-moderate did not result in discontinuation of treatment with pamrevlumab, and did not result in the use of prophylaxis for subsequent infusions.

The favorable experience with pamrevlumab to date does not exclude the possibility of more severe infusion reactions occurring in future subjects.

This is the first clinical study of pamrevlumab in DMD. There are currently no confirmed benefits to subjects with DMD treated with pamrevlumab. However, a potential benefit of treatment with pamrevlumab is indicated in preclinical models of DMD and previous clinical studies of pamrevlumab in other indications where CTGF is also associated with disease progression.

Dose regimens equal to or exceeding 35 mg/kg have been implemented in other indications in adult subjects. The objective of these studies was to inhibit bioactive CTGF, which is associated with disease progression in a number of indications. Please refer to the Investigator's Brochure for a comprehensive summary of efficacy, safety, and exposure data.

The current study will explore the clinical relevance of CTGF inhibition, as indicated in preclinical models, in DMD patients.

2.5 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Periods

Pamrevlumab is administered as an IV infusion at a dose of 35 mg/kg every two weeks for two years (Day 0 to Week 104). The dose, frequency and route of administration correspond with dose regimens that were well tolerated and possibly associated with efficacy in clinical studies in adults with IPF and pancreatic cancer. In both of these indications pamrevlumab was

administered at doses that included the targeted dose regimen for the current study (35 mg/kg bodyweight) and greater (45 mg/kg bodyweight). These doses were not associated with dose limiting toxicity.

The overall objective of all of these studies, including the current study, is to provide a dose associated with clinically relevant CTGF blockade to impede progression of serious disease states. Body weight-related dosing and utilization of a dose no greater than the maximal dose used in adults are expected to ensure that systemic exposure in the targeted pediatric population will not exceed the systemic exposure achieved in adults.

PK assessments will be done during the course of the study and facilitate ongoing monitoring of exposure to pamrevlumab during the course of the study.

The planned treatment duration is no longer than total treatment periods achieved in previous studies with pamrevlumab.

The duration of treatment of the current study is also similar to the duration of other studies in DMD and is expected to provide sufficient basis to evaluate potential benefit in the targeted pediatric population with DMD.

2.6 Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents. Detailed information regarding study conduct is found in Sections 10, 11, 12, and 13.

2.7 Population to be Studied

Non-ambulatory adolescents and adults with DMD will be enrolled in this trial. A detailed inclusion/exclusion list is provided in Section 5.

3 OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is to estimate pamrevlumab's efficacy in non- ambulatory subjects with DMD.

3.2 Secondary Objectives

The following are the secondary objectives of this trial:

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

4 STUDY DESIGN

4.1 Endpoints and Assessments

4.1.1 Primary Endpoint

The primary endpoint is the annual change from baseline to Week 104 in percent predicted forced vital capacity (FVC) during treatment with pamrevlumab.

4.1.2 Secondary Endpoints

The following are the secondary endpoints:

- Change from baseline to Week 104 in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow
- Change in LVEF from baseline to Week 104
- Change from baseline to Week 104 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 104 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 104 in cardiac fibrosis score assessed by MRI
- Change from baseline to Week 104 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

4.1.3 Exploratory, Pharmacokinetic and Pharmacodynamic Outcome Measures

Exploratory outcome measures for this trial are:

In the first 12 subjects to have complete PK/PD samples:

- Pharmacokinetic (PK) profile of pamrevlumab (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$)
    - In the overall population
    - In subjects 12 to 16 years of age, inclusive
    - In subjects older than 16 years
    - Comparison of PK profiles across age groups
- Plasma and urine CTGF
- Creatine kinase (CK)
- Circulating biomarkers

4.1.4 Safety Assessments

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

4.2 Trial Overview

This study will be an open-label, single arm study that will initially enroll approximately 22 subjects. Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for up to 104 weeks. An interim analysis will be conducted after at least 12 subjects have completed 1 year of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow) on a continuous basis.

Upon completion of treatment or premature discontinuation from the trial, subjects will be asked to return to the investigative site to complete final safety and efficacy assessments.

4.3 Study Treatment

4.3.1 Dose and Schedule

Each subject will receive pamrevlumab (35 mg/kg) intravenously every 2 weeks (q2w). See Section 6 for detailed information on study drug formulation, storage, and administration.

4.3.2 Rationale for Dose and Schedule

The pamrevlumab dose is based on results of a study in adult subjects with pancreatic cancer. In that study (Section 2.3.4.1), minimum pamrevlumab blood levels (C_{min})

≥150 mcg/mL were associated with increased median survival and 1 year survival compared to subjects with C_{min} <150 mcg/mL. Given the apparent threshold effect for increased benefit when minimal pamrevlumab exposure is ≥150 mcg/mL and based on PK analysis using these data, the planned dose of 35 mg/kg administered every 2 weeks is projected to achieve this minimum exposure in the targeted DMD study population.

4.4 Concomitant Medications, Procedures and Nondrug Therapies

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy.

Investigational agents, and those that receive marketing authorization during this trial, or approved product for DMD (e.g. eteplirsen) are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

Concomitant medications (any prescription and/or over-the-counter [OTC] preparation) and procedures or nondrug therapies (e.g., physical therapy or acupuncture) used by a subject while participating in this clinical trial must be recorded from the Screening Visit through the End-of-Study Visit.

Questions regarding potential impact of concomitant medications on evaluability of subjects should be addressed to the attention of the FibroGen Medical Monitor.

4.4.1 Contraception

Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy of a partner must be reported (Section 8.3.6).

4.5 Safety Plan

An ongoing safety review is facilitated by the unblinded nature of the study. FibroGen will review safety data and will communicate the results of these reviews to investigators by email or teleconference on a regular basis. In addition, FibroGen will review safety experience with investigators during teleconferences that will be held at least quarterly and include the conclusions of the Data Monitoring Committee's (DMC) latest data review.

FibroGen will notify investigators immediately if a new safety risk is identified.

4.6 Data Monitoring Committee

A DMC will be utilized and will be composed of external experts. Composition and responsibilities of the DMC are defined in a separate DMC charter.

DMC responsibilities include review of safety data, and may include available pharmacokinetic data, and pulmonary function tests.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. At least one historical FVC % predicted value within 18 months of baseline
10. Left ventricular ejection fraction >45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Subjects currently receiving heart failure cardiac medications (e.g. angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /μL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤3 x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN

17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after the last dose of study drug

5.2 Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 104 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 104 weeks
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

5.3 Subject Withdrawal

Subjects may withdraw from the study at any time.

The investigator may remove a subject from study treatment for the following reasons:

- Adverse events, which in the opinion of the Principal Investigator and/or FibroGen preclude further study drug dosing
- Nonadherence to protocol-defined procedures, in particular missing of 3 or more sequential study drug infusions
- Not available for safety assessments

Subjects who discontinue the study early should be strongly encouraged to complete the evaluations described in Section 7.1.3.

5.4 Replacement of Subjects

Subjects may be replaced in this study if a subject's participation is not terminated due to safety or tolerability issues and is replaced prior to completion of targeted recruitment into the study. Replacement decisions will be made between the sponsor and investigator on a case-by-case basis.

5.5 Study Termination

This trial can be terminated by the sponsor at any time for any reason.

6 STUDY DRUG/TREATMENT SUPPLY

6.1 FibroGen Investigational Product

Pamrevlumab is a fully human IgG_1 kappa monoclonal antibody that binds to CTGF.

6.1.1 Formulation

Pamrevlumab is supplied in single-use glass vials containing 10 mL of a sterile, preservative-free solution. The solution is composed of 10 mg/mL pamrevlumab, 1.60 mg/mL l-histidine, 3.08 mg/mL l-histidine HCl, 8.01 mg/mL sodium chloride and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0. If different vial sizes or new formulations are introduced during the course of the study, updates to formulation, storage, etc. will be provided through an amendment to the Pharmacy Manual and investigative site staff training.

6.1.2 Storage

Vials of pamrevlumab must be stored refrigerated (2°C to 8°C), in a temperature- controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation.

6.1.3 Preparation of Dose for Administration

The dose of pamrevlumab (35 mg/kg) for the first infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken every 3 months thereafter. Pamrevlumab may be administered undiluted or, for convenience of infusion, may be diluted with 0.9% Sodium Chloride Injection according to the Dose Preparation Instructions in the Study Reference Investigational Product (IP) Manual.

Pamrevlumab will be administered as soon as possible after release from the site's pharmacy and within 24 hours of preparation. Pamrevlumab will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

6.1.4 Administration

Study Drug	Dose	Route	Infusion Rate	Schedule
Pamrevlumab	35 mg/kg	IV	Not to exceed 150 cc/hour	Every 2 weeks
DO NOT ADMINISTER PAMREVLUMAB AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.				

Subjects who weigh more than 117 kg will receive the maximum allowed dose of 4.1 g. For this study, the overall rate of infusion for the prepared study drug should not exceed 150 cc/hour. Adjustments may be made to further slow the rate of infusion (infusing less than 150 cc/hour) in accordance with the investigator's clinical judgement. Subjects should be carefully monitored

for reaction during the first infusion with a physician available as needed. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation. The IV access should remain in place and be maintained per site procedures until the end of this post treatment observation period.If a subject has an infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences an infusion reaction and continues pamrevlumab dosing, a physician must be immediately available during subsequent infusions and observation periods until the subject does not have any infusion reaction for three sequential infusions.

Premedication, such as antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are not normally administered before infusions of pamrevlumab.

Premedication may be used for subjects who experience infusion reactions at the discretion of the investigator after discussion with the Medical Monitor.

Pamrevlumab will be administered in a hospital or ambulatory setting with adequate facilities for managing medical emergencies for at least three infusions to confirm the subject does not have an infusion reaction. The study site must have trained staff and medications for the treatment of acute reactions, including anaphylaxis, immediately available. There is no specific treatment for a pamrevlumab overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

FibroGen may consider the use of properly trained home health care staff to administer the pamrevlumab infusions in the future and corresponding study assessments during the conduct of the study, consistent with institutional regulations and policies.

7 ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

7.1 Study Procedures by Visit

All study procedures and assessments will be performed in accordance with the Schedule of Assessments presented in Section 16.

For all potential subjects, screening procedures required to determine subject eligibility will be performed within 28 days prior to Day 0 (first infusion of pamrevlumab).

Potential subjects may be re-screened if initial screening procedures lie outside the 28-day screening period prior to planned study entry.

Subject's eligibility for this study will be reviewed and approved by Sponsor's medical monitor prior to subject enrollment.

The following assessments are relevant to the assessment of efficacy: pulmonary function tests (FVC, mean inspiratory flow (MIF), peak expiratory flow), Brooke Upper Extremity Rating Scale, Performance of the Upper Limb, pinch strength, grip strength, cardiac MRI, and muscle MRI. Refer to the Study Reference Manual for details.

Approved windows for performing study assessments are defined in the following sections.

7.1.1 Screening Period (no earlier than Day -28)

Assessments to be conducted during the screening period are presented in Appendix 1.

Screening assessments may be completed over several visits during the screening period. It is recommended that the less invasive screening assessments be performed first upon completion of the signed Informed Consent and/or Assent Form [ICF] (demographics, medical history, blood draws, electrocardiogram [ECG], vital signs (includes body weight and height), physical exam, pulmonary function tests (PFTs), and then followed by the more rigorous screening assessments (i.e., muscle function tests, cardiac MRI).

A cardiac MRI performed within 3 months prior to Day 0 (start of dosing) is acceptable to confirm eligibility based on the LVEF study entry criterion and as baseline cardiac MRI. If an historic MRI is not available, a cardiac MRI must be performed during the Screening Period.

An upper arm muscle MRI is not required to determine subject eligibility at screening, but may be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Muscle and pulmonary function tests (PFTs) will be performed during the screening period. Muscle function and PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.

If the subject cannot perform adequately due to illness (e.g. sinusitis, etc.) then the PFTs should be delayed until the subject can reliably perform the assessment within the 28-day screening window.

In addition, an exploratory blood sample will be drawn for analysis of circulating biomarkers of fibrosis and specific muscle miRNAs (dystromirs) prior to first pamrevlumab infusion.

7.1.2 Dosing Period

The dosing period begins on the first day of dosing with study treatment (Day 0) and continues through Week 104. Subjects will receive study drug every 2 weeks.

The visit window for all dosing visits is ±2 days. Visits should be scheduled based on the previous visit, not the baseline visit.

Assessments and procedures to be performed during the dosing period are presented in Section 16.

Muscle or pulmonary function tests that cannot be performed or produce inadequate results according to test procedures during a specified visit should be performed by the next scheduled dosing visit.

Both cardiac and muscle MRIs may be performed within ±2 weeks of the specified visit.

Blood samples will be drawn for pharmacokinetic analysis according to the schedule in Appendix 4. Blood draws to be collected on non-dosing days may be collected within ±1 day as outlined in Appendix 4.

7.1.3 End of Treatment

Assessments and procedures to be conducted after the last dose of study drug are presented in Appendix 3.

The end of treatment cardiac and muscle MRIs may be performed any time from Week 104/EOT to Week 106/EOS (End of Study) visit.

Subjects who complete 104 weeks of treatment will have their end of treatment assessments performed at the Week 104/EOT visit.

7.1.4 Early Withdrawal from Treatment and Safety Follow-up Period

Subjects who prematurely discontinue the study should be strongly encouraged to complete the final efficacy evaluations scheduled for Week 104/EOT as applicable, and the safety follow-up evaluations scheduled for the Week 106/EOS visit (4 weeks following the last dose).

7.1.5 Safety Follow-Up Period

For all subjects, the final safety assessments should be completed at the Week 106/EOS visit, 4 weeks (±7 days) after the last dose of pamrevlumab.

7.1.6 Missed Visits

Every attempt must be made to complete all study visits as outlined in the Schedules of Assessments. Missed infusions will not be replaced. If a subject misses a scheduled efficacy assessment, the assessment should be performed as soon after the missed visit as feasible and within the windows specified above.

7.1.7 Unscheduled Visits

Unscheduled Visit assessments may be required at the discretion of the investigator.

7.2 Assessments

Please refer to the Schedules of Assessments (Section 16) for the scope and timing of assessments. Please refer to the Laboratory Manual for details regarding laboratory sample collection and processing; and the Study Reference Manual for details regarding the conduct of functional tests and MRIs.

7.2.1 Pulmonary Function Tests

The following pulmonary function tests (PFTs) will be performed to assess changes in lung function: forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow rate (PEF; PEFR), forced expiratory volume in 1 second (FEV1), and peak cough flow (Mayer, 2015, Miller, 2005).

7.2.2 Muscle Strength and Functional Measurements

The following assessments will be performed to assess changes in upper extremity strength and function: Brooke Upper Extremity Rating Scale (Brooke Scale), Performance of the Upper Limb (PUL), Grip Test, and Pinch Strength Test.

7.2.3 Cardiac MRI

Cardiac MRIs will be performed as per Section 16 to assess changes in left ventricular ejection fraction (LVEF) and presence of late gadolinium enhancement (LGE), a marker for myocardial fibrosis.

7.2.4 Muscle MRI

An upper arm muscle MRI at screening, will be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Upper arm (bicep) muscle MRIs will be performed as per Section 16.

7.2.5 Quality of Life Questionnaire

Pediatrics Outcomes Data Collection Instrument (PODCI) Quality Outcome Questionnaire will be performed to assess if treatment with pamrevlumab improves quality of life.

7.2.6 Vital Signs and Physical Examinations

A physical examination will be performed at screening and baseline (Day 0), approximately every 12 weeks and at Week 104/EOT. Complete physical exams will be performed at screening, Week 48, and Week 104/EOT. Other examinations may be disease-specific or problem-oriented examinations.

Vital signs (pulse, respiration, sitting blood pressure, and temperature) will be collected at screening and at all visits. During infusion visits, vital signs will be collected prior to start of each infusion, within 15 minutes of the end of each infusion, and within 15 minutes of the completion of the post-infusion observation period.

7.2.7 Laboratory Assessments

All laboratory tests of blood and/or urine specimens will be performed at a central laboratory or FibroGen, as appropriate. A Central Laboratory Manual with instructions on specimen

collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local clinical laboratories will be used to assess and facilitate the management of adverse events and to provide usual standard of care (including blood draws required prior to MRIs). Local clinical laboratory data will not be collected in the study database except for hematocrit values provided with imaging data.

7.2.7.1 Safety Assessments

Blood samples will be 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.

Safety labs will be drawn at the site's local lab prior to MRIs to ensure there is no contraindication to MRI. Hematocrit should be included in the local lab draw as these results are required to assess fibrosis and will be provided to the central imaging vendor along with the MRI scans. Details are included in the Imaging Manual.

7.2.7.2 Pharmacokinetics

Plasma concentrations of pamrevlumab will be determined on Day 0 pre-dose and within 1 hour post infusion, then on Days 2, 4, 7, 10, and 14. The Day 14 sample should be on the same day of, but prior to the start of the next infusion of study drug.

Day 2, 4, 7, and 10 PK assessments represent target days following the first dose; however, actual sample collection time of up to ±1 day of the target time is acceptable as

long as the actual time of dosing and actual time of each sample collection are recorded accurately.

At Weeks 26 and 52, trough pamrevlumab levels (C_{min}) will be determined prior to study drug infusion.

PK samples will also be drawn within 60 minutes of infusion completion at Week 52.

7.2.7.3 Plasma and Urine CTGF

Plasma and urine samples will be analyzed for CTGF concentrations from samples taken as described in Appendix 4.

7.2.7.4 HAHA

Blood samples will be drawn for analysis of human anti-human antibody (HAHA) according to the schedule in Appendix 4.

7.2.7.5 Biomarkers

Blood samples will be drawn for analysis of biomarkers. The exact biomarkers will be based on current scientific knowledge regarding CTGF, pamrevlumab and DMD at the time the tests are performed. No genetic testing will be performed.

8 ASSESSMENT OF SAFETY

8.1 Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Section 16. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the Study Drug.

8.2 Definitions

8.2.1 Definition of an Adverse Event (AE)

For the purpose of this study, an AE is any untoward medical occurrence that occurred in the protocol-specified AE reporting period, and which does not necessarily have a causal relationship with the study drug. An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the

protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.3.1).

8.2.2 Definition of a Serious Adverse Event (SAE)

A **serious adverse event** is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.2.3 Definition of an Infusion Reaction

Infusion reactions are immunologic reactions to an infused protein, and are different from events resulting from the process of infusing the protein (e.g., infusion site bruise) and are different from adverse events due to the infused protein's intended or unintended pharmacologic effects.

8.2.3.1 Acute Infusion Reaction

An acute infusion reaction is one that meets both of the following criteria:

1. Occurs during or within 1 hour after infusion; and
2. Clinical manifestations consistent with:
    - IgE-mediated and non-IgE mediated hypersensitivity reactions, including but not limited to urticaria, skin rashes, angioedema, laryngeal edema, bronchospasm, gastrointestinal symptoms and hypotension; or
    - Cytokine release syndrome, including but not limited to fever, respiratory symptoms without the presence of wheezing, tremors, chills, flushing, pruritus, changes in blood pressure, dyspnea, chest discomfort, back pain, nausea, vomiting, diarrhea, and skin rashes.

8.2.3.2 Delayed Infusion Reaction

A delayed infusion reaction is one that meets both of the following criteria:

1. Occurs ≥1 hour after the infusion
2. Clinical manifestations as described above.

8.2.3.3 Reporting Possible and Confirmed Infusion Reactions

Both acute and delayed infusion reactions will be captured as AEs and also be reported to the medical monitor within 24 hours. See Study Reference Manual for additional details.

8.2.4 Special Situations

Certain safety events, called 'Special Situations' that occur in association with the study drug(s) include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product

- Medication error involving the medicinal product (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

Special Situations will be reported to the sponsor or designated vendor within 24 hours on a Medication Error report form. See Study Reference Manual for details.

8.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 4 weeks after the last dose of study drug, except for pregnancy reporting (Section 8.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5).

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever is possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff.

New indications for medications started during the AE reporting period (i.e., after informed consent is obtained until 4 weeks after the last dose of study drug) will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the Investigator to meet the specified criteria.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug

- Other treatment required
- Determination of "seriousness"

8.3.3 Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 4.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild**: Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; ; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death:** Fatal AE.

8.3.4 Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- **Related:**
    - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re- occurs with re-administration of study drug; another example is a typical drug-

related medical condition such as a rash that occurred shortly after first dose of study drug.

- **Not Related:**
  - The event represents a pre-existing underlying disease that has not worsened on study
  - The event has the same characteristics of a known side-effect associated with a co-medication
  - The event is an anticipated medical condition of anticipated severity for the study population
  - The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5 Reporting Serious Adverse Events on the SAE Report Form

An SAE must be reported to the Sponsor and/or its designated safety management vendor within 24 hours of becoming aware of the SAE.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

The contact information for SAE reporting is as follows:

U.S. Toll-Free Fax Number: [redacted]

Email: [redacted]

8.3.5.1 Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2 Deaths

The investigator will report the fatal or life-threatening event immediately to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to

4 weeks after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. Additionally, the site must complete the appropriate CRF page.

8.3.6 Pregnancies: Reporting and Follow-up of Subjects

The outcome of all pregnancies should be followed up and documented as described. Consent must be obtained from male subject's partner to collect information related to the pregnancy and outcome (and will be handled on a case-by-case basis with IRB/IEC approval). A Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

8.3.7 Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all laboratory results throughout the study in a timely manner, and determine whether any abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

This study tests the hypothesis of whether pamrevlumab can attenuate the annual decline in FVC in non-ambulatory DMD patients. A total of 22 subjects is planned to achieve 80% power to test the null hypothesis of change in percent predicted FVC of -5% against the alternative hypothesis, assuming a mean change of -2% and standard deviation of 5% based on 2-sided one sample t-test at 0.05 significance level. The hypotheses are:

H_0: change in percent predicted FVC less than or equal to -5%

H_a: change in percent predicted FVC greater than -5%.

The primary efficacy endpoint will be met if the annual change in percent predicted FVC is greater than -5% at the end of the study (lower bound of 2-sided 95% confidence interval is greater than -5%).

9.2 Analysis Populations

9.2.1 Safety Population

The Safety Population will consist of all subjects who have received any dose of pamrevlumab. This population is also defined as the intent-to-treat (ITT) population.

9.2.2 Full Analysis Set Population

The Full Analysis Set Population (FAS) will consist of all subjects in the Safety Population who have at least one evaluable post-baseline FVC assessment.

9.3 Statistical Analysis

9.3.1 General Considerations

Descriptive summaries will be provided for all study parameters including baseline characteristics, safety, efficacy, pharmacokinetic and pharmacodynamic parameters. Continuous variables will be reported using number of subjects, mean, standard deviation or standard error, median, minimum, and maximum. In general, standard deviation is provided to describe the distribution of a parameter, such as baseline, safety, and PK/PD parameters; while standard error is provided for efficacy analysis to facilitate

between-group comparisons. Geometric mean will be included for PK/PD variables. Categorical variables will be reported by the frequency and percentage of subjects within each outcome category. Two-sided 95% confidence intervals will be presented for key efficacy parameters and two-sided 90% confidence intervals for PK/PD parameters. All statistical tests will be performed at an α=0.05 level of significance, using two-sided tests, unless otherwise stated. Assessments as well as derived parameters will be presented in data listings for all subjects in the ITT/Safety Population.

9.3.2 Subject Enrollment and Disposition

The number of subjects in each study population as well as subject completion status and reasons for early discontinuation will be summarized.

9.3.3 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, and quality of life parameters.

9.4 Efficacy Analyses

Efficacy analyses will be based on the FAS population. Rules of handling missing data will be described in the Statistical Analysis Plan (SAP). Analyses based on observed data will be performed for sensitivity evaluation.

9.4.1 Primary Endpoint

The primary endpoint is the annual change in percent predicted FVC during treatment with pamrevlumab. The annual change in percent predicted FVC for each subject will be analyzed using one sample t-test. The mean annual change in percent predicted FVC and the corresponding 2-sided 95% confidence interval will be presented.

9.4.2 Analyses of Other PFT Parameters

Changes from baseline to Week 104 in other PFT parameters will be estimated similarly; details of missing data handling will be described in the statistical analysis plan (SAP).

9.4.3 Analysis of PUL Parameters, Pinch and Grip Strength, Brooke Scale

Change from baseline to Week 104 in hand/arm function and strength will be analyzed. In order to evaluate overall effect, composite scores may be explored. Two-sided 95% confidence intervals will be presented.

9.4.4 Analysis of LVEF, Cardiac Fibrosis, and Muscle Fat and Fibrosis

Changes from baseline in LVEF, cardiac fibrosis, and muscle fat and fibrosis will be summarized descriptively based on available data at Week 104.

9.4.5 Analysis of PODCI Quality Outcome Data

Changes from baseline in modified PODCI scores of subjects will be summarized descriptively based on available data at each assessment time point.

9.4.6 Pharmacokinetic Analyses

Pamrevlumab concentrations and derived PK parameters (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$) will be summarized using descriptive statistics. Pharmacokinetic analysis will be performed using commercial software such as WinNonlin.

Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the

PK parameters (1) in the overall population, (2) in subjects 12 to 16 years of age, and (3) in subjects older than 16 years. Comparison of PK parameters between the age groups will be

performed. Trough values, measured at several time points during the course of the study, will be compared to determine steady state and accumulation.

9.4.7 Safety Analyses

Safety analyses will include summary of adverse events, prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs). In general, safety data will only be summarized descriptively and no inferential statistical procedures will be applied.

For data summarization, adverse events will be classified into standard terminology using a coding thesaurus (MedDRA), and reported by system organ class and preferred term.

Treatment-emergent adverse events will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Deaths, SAEs, and AEs leading to study or treatment discontinuation, and infusion reactions will be listed or tabulated separately.

Clinically significant changes from baseline in vital signs, laboratory tests, and ECG will be identified. Shift tables will summarize changes in selected laboratory measures.

All safety analyses will be performed based on the Safety Population.

9.5 Administrative Analyses

In this open-label exploratory study, safety will be monitored on an ongoing basis.

The DMC will review all safety data, which may include available pharmacokinetic data, and pulmonary function tests.

10 DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the International Conference on Harmonisation (ICH) E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IVRS [or IWRS], clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The investigator must also permit the U.S. FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the investigator is notified of an inspection pertaining to this study by the U.S. FDA or other applicable regulatory authorities, the investigator must notify FibroGen immediately.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents

11.2 Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

12 ETHICS

12.1 Ethical Considerations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

12.2 Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

12.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent (ICF) and/or Assent Form from the subject or written Informed Consent Form signed by the subject's legally authorized representative, as applicable. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a

HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

12.4 Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

13 DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs/eCRFs and resolved queries.

13.2 Data Collection, Handling, and Verification

All required data will either be entered onto CRFs/eCRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with a full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion, ensuring that all data is verifiable with source documents.

14 PUBLICATION POLICY

A detailed explanation of FibroGen's publication policy is described in the Clinical Trial Agreement.

15 REFERENCES

Au CG, Butler TL, Sherwood MC, Egan JR, North KN, Winlaw DS (2011) Increased connective tissue growth factor associated with cardiac fibrosis in the *mdx* mouse model of dystrophic cardiomyopathy. Int J Exp Pathol 92: (1):57-65

Bushby K, Finkel R, Birnkrant DJ, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 9: (1):77-93

Desguerre I, Mayer M, Leturcq F, Barbet JP, Gherardi RK, Christov C (2009) Endomysial fibrosis in Duchenne muscular dystrophy: a marker of poor outcome associated with macrophage alternative activation. J Neuropathol Exp Neurol 68: (7):762-773

Emery AE (1991) Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord 1: (1):19-29

Kharraz Y, Guerra J, Pessina P, Serrano AL, Munoz-Canoves P (2014) Understanding the process of fibrosis in Duchenne muscular dystrophy. Biomed Res Int **2014:**965631

Mayer OH, Finkel RS, Rummey C, et al. (2015) Characterization of pulmonary function in Duchenne Muscular Dystrophy. Pediatr Pulmonol 50: (5):487-494

McKim DA, Katz SL, Barrowman N, Ni A, LeBlanc C (2012) Lung volume recruitment slows pulmonary function decline in Duchenne muscular dystrophy. Archives of Physical Medicine and Rehabilitation 93: (7):1117-1122

Miller MR, Hankinson J, Brusasco V, et al. (2005) Standardisation of spirometry. Eur Respir J 26: (2):319-338

Morales MG, Cabello-Verrugio C, Santander C, Cabrera D, Goldschmeding R, Brandan E (2011) CTGF/CCN-2 over-expression can directly induce features of skeletal muscle dystrophy. J Pathol 225: (4):490-501

Morales MG, Gutierrez J, Cabello-Verrugio C, et al. (2013) Reducing CTGF/CCN2 slows down *mdx* muscle dystrophy and improves cell therapy. Hum Mol Genet 22: (24):4938-4951

Pessina P, Cabrera D, Morales MG, et al. (2014) Novel and optimized strategies for inducing fibrosis in vivo: Focus on Duchenne Muscular Dystrophy. Skelet Muscle 4:7

Phillips MF, Quinlivan RC, Edwards RH, Calverley PM (2001) Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med 164: (12):2191-2194

Schram G, Fournier A, Leduc H, et al. (2013) All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 61: (9):948-954

Sun G, Haginoya K, Wu Y, et al. (2008) Connective tissue growth factor is overexpressed in muscles of human muscular dystrophy. J Neurol Sci 267: (1-2):48-56

Tandon A, Villa CR, Hor KN, et al. (2015) Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. J Am Heart Assoc 4: (4):e001338

Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH (2001) Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. Arch Dis Child 84: (6):521-524

Vial C, Zuniga LM, Cabello-Verrugio C, Canon P, Fadic R, Brandan E (2008) Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. Journal of Cellular Physiology 215: (2):410-421

16 APPENDICES

Appendix 1. Schedule of Assessments: Screening Period through Week 26

	Screening Period (4 Weeks)	Treatment Period (Weeks)													
		Day 0	2	4	6	8	10	12	14	16	18	20	22	24	26
Informed Consent & Assent	X														
Inclusion/ Exclusion	X														
Demographics	X														
Medical History	X														
Clinical laboratory assessments[b,i]	X			X		X		X						X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X							X						X	
Electrocardiogram	X														
Physical Examination[e]	X	X						X						X	
Muscle function tests[f]	X	X						X						X	
Pulmonary function tests[g]	X	X						X						X	
Cardiac MRI[i]	X[i]														
Muscle MRI[i]	X[i]														
Specialty labs[h]		X	X												X
Pamrevlumab infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire		X													X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting BP, temperature) to be collected at every visit, and pre-infusion, within 15 minutes of completion, and within 15 minutes of completing observation period.
d. Weight and height (estimated from ulna length) to be measured at screening and every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at screening. Other exams may be disease specific or problem oriented.
f. Muscle function tests (MFT): Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test. MFTs will be performed during the screening period. MFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
g. Pulmonary function tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow. PFTs will be performed during the screening period. PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Baseline muscle MRI may be conducted during the screening period or up to Week 4 dosing visit. Local safety labs are required prior to the MRIs, and must include hematocrit.

Appendix 2. Schedule of Assessments: Week 28 through Week 58

	Treatment Period (Weeks)													
	28	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**	**54,56, 58**
Clinical laboratory assessments[b,i]					X						X			
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]					X						X			
Electrocardiogram													X	
Physical Examination[e]					X						X			
Muscle function tests[f]					X						X			
Pulmonary function tests[g]					X						X			
Cardiac MRI[i]													X	
Muscle MRI[i]													X	
Specialty labs[h]													X	
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire													X	

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured at screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 48. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs are required prior to the MRIs and must include hematocrit.

Appendix 3. Schedule of Assessments: Week 60 through Week 106/EOS

Assessment[a]	Treatment Period (Weeks)									
	60	**62,64, 66,68,70**	**72**	**74,76, 78,80,82**	**84**	**86,88,90, 92,94**	**96**	**98,100, 102**	**104/EOT**	**106/EOS**
Clinical laboratory assessments[b,i]	X		X		X		X			X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X		X		X		X			
Electrocardiogram									X	
Physical Examination[e]	X		X		X				X	
Muscle function tests[f]	X		X		X				X	
Pulmonary function tests[g]	X		X		X				X	
Cardiac MRI[i]									X	
Muscle MRI[i]									X	
Specialty labs[h]									X	X
Pamrevlumab infusion	X	X	X	X	X	X	X	X		
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome									X	

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured in screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 104/EOT. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 4 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs required prior to the MRIs and must include hematocrit.

Appendix 4. Specialty Lab Schedule

		Treatment Period								EOT	Safety Follow-up
Sample	**Timepoint**	**Day 0**	**Day 2 ±1 day**	**Day 4 ±1 day**	**Day 7 ±1 day**	**Day 10 ±1 day**	**Week 2**	**Week 26**	**Week 52**	**Week 104/EOT**	**Week 106/EOS (4 weeks after last dose)**
Pamrevlumab PK[a]	Before infusion	X					X	X	X		
	Within 1 hour after infusion	X							X		
	Time point sample (no infusion)		X	X	X	X					
HAHA[b]	Predose (when applicable)	X									X
CTGF[c]	Predose (when applicable)	X								X	
Exploratory[d]	Predose (when applicable)	X							X	X	

Abbreviations: CTGF = connective tissue growth factor; ET = early termination; HAHA = human anti-human antibody; PK = pharmacokinetic

a. Approximately 1-2 mL of blood will be collected for each measurement of pamrevlumab PK.
b. Approximately 1 mL of blood will be collected for each measurement of HAHA.
c. Blood and urine samples will be collected. Approximately 1 mL of blood and 0.5 mL of urine will be collected for each measurement of CTGF.
d. Approximately 5 mL of blood will be collected for each exploratory sample.

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
PROTOCOL NUMBER:	FGCL-3019-079
PHASE:	2
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	126630
STUDY DRUG:	Pamrevlumab (FG-3019)
INDICATION:	Duchenne Muscular Dystrophy
FIBROGEN MEDICAL MONITOR:	[redacted] FibroGen, Inc. [redacted] Telephone: Mobile: E-mail Address:
ORIGINAL PROTOCOL:	16 June 2015
AMENDMENT 1.0:	31 August 2015
AMENDMENT 2.0:	06 May 2016
AMENDMENT 3.0:	09 December 2016
AMENDMENT 4.0:	10 July 2017
AMENDMENT 5.0:	14 November 2017

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy

FGCL-3019-079

Original: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

Amendment 3.0: 09 December 2016

Amendment 4.0: 10 July 2017

Amendment 5.0: 14 November 2017

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen's designee. Please retain the original for your study files.

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

Amendment 3.0: 09 December 2016

Amendment 4.0: 10 July 2017

Amendment 5.0: 14 November 2017

This protocol is approved by FibroGen.

[redacted]

FibroGen, Inc.

17 Nov 2017

Date

AMENDMENT 5.0: KEY CHANGES FROM AMENDMENT 4.0

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Key Change	Rationale	Sections Affected
The primary efficacy endpoint was changed from "annual change in percent predicted forced vital capacity (FVC) during treatment with pamrevlumab" to "annual change from baseline to Week 104 in percent predicted in forced vital capacity (FVC) during treatment with pamrevlumab	The study duration was changed from 2-year to 3-year, the time point of the primary efficacy will need to be clarified.	Synopsis, Protocol Section 9.1 and 9.4.1
The sentence about the analysis method ("T-test") for primary efficacy endpoint was removed.	This part will be detailed in the SAP,	Section 9.4.1
Number of subjects required for Interim analysis modified from "at least 12" to "at least 10 to 12".	Depending on study enrollment the interim analysis may be conducted with 10 subjects. Further details will be provided in the SAP.	Synopsis, Protocol Section 4.2
Clarification provided for PK sample time-point collection.	Removal of the requirement to have "complete" samples through day 14 allows for analysis to be conducted if individual samples between, but not including, Day 0 and Day 14 are missing.	Synopsis, Protocol Section 4.1.3
Extended treatment duration from 104 weeks to 156 weeks with exploratory analyses at week 156.	The study durations has been extended to collect more data.	Synopsis, Protocol Sections 2.5, 4.1.3, 4.2, 5.2, 7.1.2-7.1.5, 7.2.6, Appendix 3, Appendix 4, Appendix 5.
Modified Inclusion Criterion #10 from >45% to ≥45%.	Allows for inclusion of subjects when percentage value is rounded.	Synopsis, Protocol Section 5.1
Minor typos and formatting corrections	Formatting, typos	Throughout

PROTOCOL SYNOPSIS	
Study Title:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
Protocol Number:	FGCL-3019-079, Amendment 5.0
Investigational Product:	Pamrevlumab (FG-3019) (Recombinant fully human IgG_1 kappa monoclonal antibody to connective tissue growth factor)
Study Phase:	Phase 2
Target Population:	Non-ambulatory subjects with Duchenne muscular dystrophy (DMD)
Number of Subjects Planned:	Approximately 22 subjects will be enrolled; interim analysis may increase sample size to approximately 32
Study Centers Planned:	Approximately 10 centers

OBJECTIVES

Primary Objective

To estimate pamrevlumab's efficacy in non-ambulatory subjects with DMD

Secondary Objectives

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

ENDPOINTS/ASSESSMENTS

Efficacy

Primary Endpoint

- Annual change from baseline to Week 104 in percent predicted forced vital capacity (FVC) during treatment with pamrevlumab.

Secondary Endpoints

- Change from baseline to 104 weeks in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow

- Change in LVEF from baseline to Week 104
- Change from baseline to Week 104 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 104 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 104 in cardiac fibrosis score assessed by magnetic resonance imaging (MRI)
- Change from baseline to Week 104 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

Exploratory, Pharmacokinetics, Pharmacodynamics

- Pharmacokinetic (PK) profile of pamrevlumab (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$) [In the first 12 subjects to have PK/PD samples though Day 14]
  - In the overall population
  - In subjects 12 to 16 years of age, inclusive
  - In subjects older than 16 years
  - Comparison of PK profiles across age groups
- Plasma and urine connective tissue growth factor (CTGF)
- Creatine kinase (CK)
- Circulating biomarkers
- Exploratory analyses on primary and secondary efficacy endpoints at week 156 will be conducted at the end of the study.

Safety

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

STUDY DESIGN

This study is an open-label, single arm study which will initially enroll approximately 22 subjects. Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for up to 156 weeks. An interim analysis will be conducted after at least 10 to 12 subjects have completed 52 weeks of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow).

STUDY PROCEDURES

Details regarding study procedures are provided as follows:
Appendix 1: Screening Period through Week 26

Appendix 2: Week 28 through Week 58
Appendix 3: Week 60 through Week 104
Appendix 4: Week 106 through Week 156/EOS
Appendix 5: Specialty Lab Schedule

MAIN SELECTION CRITERIA

Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. At least one historical FVC % predicted value within 18 months of baseline
10. Left ventricular ejection fraction ≥45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Subjects currently receiving heart failure cardiac medications (e.g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation.
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /µL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤3x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after last dose of study drug.

Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 156 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 156 weeks
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

TREATMENTS

Pamrevlumab Dose, and Mode of Administration

Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for 156 weeks. The dose of pamrevlumab (35 mg/kg) for the first infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken approximately every 3 months thereafter.

Concomitant Medications/Therapies:

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy. Investigational agents, and those that receive marketing authorization, or approved product for DMD (e.g. eteplirsen) during this trial are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed. Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

STATISTICAL METHODS

A total of 22 subjects is planned to achieve 80% power to test the null hypothesis of change in percent predicted FVC of -5% against the alternative hypothesis, assuming a mean change of -2% and standard deviation of 5%, based on a 2-sided one sample t-test

at 0.05 significance level.

The primary efficacy endpoint will be met if the annual change in percent predicted FVC is above -5% after 104 weeks of treatment with pamrevlumab (lower bound of the 2-sided 95% confidence interval is above -5%).

An interim analysis will be conducted after at least 10 to 12 subjects have completed 1 year of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

The primary efficacy endpoint is the annual change from baseline to Week 104 in percent predicted FVC during treatment with pamrevlumab. The mean annual change in percent predicted FVC and the corresponding 2-sided 95% confidence interval will be presented.

Final analysis of the primary and secondary endpoints will be described in the statistical analysis plan. Details of the interim analysis will be described in an interim analysis plan.

Pamrevlumab concentrations and derived PK parameters will be tabulated and summarized using descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters. Attainment of steady-state will be investigated.

Safety analyses will include summary of adverse events (including treatment emergent AEs, treatment emergent serious AEs, deaths, and infusion-associated AEs), prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs), and physical exams.

TABLE OF CONTENTS

LIST OF APPENDICES

2 BACKGROUND

2.1 Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G1 (IgG) kappa monoclonal antibody to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role. These diseases include liver fibrosis due to hepatitis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne muscular dystrophy (DMD). Pamrevlumab (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. Pamrevlumab contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2 Duchenne Muscle Dystrophy

Duchenne muscular dystrophy (DMD) is usually inherited in an X-linked recessive fashion, but it can occur as a result of spontaneous mutation in boys from families without a known history of the condition. On the basis of some 40 studies including several million male births, incidence at birth of Duchenne muscular dystrophy is around 1:3300, and its prevalence in the population (in terms of the total male population) is around 1:16500 (Emery, 1991).

DMD is a result of mutations (mainly deletions) in the dystrophin gene (DMD; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration with loss of independent ambulation by the age of 13 years (Bushby, 2010).

In skeletal muscles of DMD patients constant myofiber breakdown results in persistent activation of myofibroblasts and altered production of extracellular matrix (ECM) resulting in extensive fibrosis. Muscle fibrosis is the only myo-pathologic parameter that significantly correlated with poor motor outcome as assessed by quadriceps muscle strength, manual muscle testing of upper and lower limbs, and age at ambulation loss (Desguerre, 2009).

Patients with DMD are generally wheelchair bound before they develop significant respiratory muscle weakness. Respiratory complications are the primary cause of morbidity and mortality in DMD as progressive respiratory muscle weakness leads to hypoventilation and/or recurrent atelectasis and pneumonia, secondary to decreased cough effectiveness (McKim, 2012).

After age 10 to 14, patients gradually begin to lose respiratory muscle function based on pulmonary function tests (PFTs) such as forced vital capacity (FVC). The median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001, Tangsrud, 2001).

Because of improvements in respiratory care, cardiac dysfunction is now a leading cause of morbidity and mortality in DMD patients (Schram, 2013). Progressive myocardial fibrosis, as detected by late gadolinium enhancement (LGE), is strongly correlated with the left ventricular ejection fraction (LVEF) decline in Duchenne muscular dystrophy patients. Longer steroid treatment duration is associated with a lower age-related increase in myocardial fibrosis burden (Tandon, 2015).

2.2.1 Relevance of Connective Tissue Growth Factor (CTGF) in DMD

Connective tissue growth factor (CTGF) is a nonstructural regulatory protein present in the extracellular matrix that has an important role in fibrosis. Skeletal muscle from DMD patients, dystrophic dogs, and mdx mice all show elevated levels of CTGF (Sun, 2008).

CTGF can reproduce or amplify the effects of TGFβ on fibrosis by inducing collagen type 1, α5 integrin, and fibronectin much more potently than TGFβ in fibroblasts (Kharraz, 2014).

Comparison of mdx mice with normal or genetically depleted levels of CTGF revealed that exercised mice with reduced CTGF developed less fibrosis and exhibited better muscle strength than mice with normal levels of CTGF (Morales, 2013). In culture, both myoblasts and myotubes were shown to express and secrete CTGF to the medium, and respond to the growth factor by increasing the extracellular matrix constituents, partially inhibiting myoblasts differentiation and inducing myoblasts dedifferentiation (Vial, 2008).

In DMD, the role of CTGF might extend well beyond replacement fibrosis secondary to loss of muscle fibers, since its overexpression in skeletal muscle could by itself induce a dystrophic phenotype (Morales, 2013).

A major feature of the hearts of DMD patients is cardiac fibrosis. Cardiac fibrosis is associated with increased CTGF expression in the mdx mouse heart. CTGF may be a key mediator of early and persistent fibrosis in dystrophic cardiomyopathy (Au, 2011).

CTGF is critically involved in several chronic fibro-degenerative diseases. Pamrevlumab treatment has been shown to positively the affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.

2.3 Summary of Relevant Findings from Nonclinical and Clinical Trials

Please refer to the most recent version of pamrevlumab Investigator's Brochure.

2.3.1 Nonclinical Studies

In DMD, the genetic loss of the cytoskeletal protein dystrophin results in muscle damage that, leads to progressive replacement of muscle with fibrotic and fat tissue. This progressive muscle damage can be recapitulated in the DMD mouse model (mdx), and accelerated by muscle usage (Pessina, 2014).

As was observed with genetic depletion of CTGF, pharmacologic inhibition of active CTGF in mdx mice by treatment with pamrevlumab resulted in reduced fibrosis and skeletal muscle damage, as well as improved preservation of skeletal muscle strength in isolated muscles. The pamrevlumab treated mdx mice were also subjected to a test of exercise endurance, in which they showed better performance than mdx mice injected with control IgG (Morales, 2013).

Pamrevlumab treatment of mdx mice was associated with decreased skeletal muscle damage and fibrosis, decreased collagen III and fibronectin expression, decreased plasma creatine kinase (CK) (Morales, 2013), and increased isometric force of skeletal muscle (Morales, 2011).

2.3.2 Pharmacokinetics

Key findings are summarized below from Phase 1 and 2 studies investigating the pharmacokinetics (PK) of pamrevlumab in subjects with diabetic kidney disease, idiopathic pulmonary fibrosis, liver fibrosis and pancreatic cancer:

- Pamrevlumab was administered over the dose range of 3 to 45 mg/kg every 2 weeks, every 3 weeks, and 17.5 to 22.5 mg/kg weekly.
- Pamrevlumab exposure (e.g., mean/median Cmax and Cmin, area under the curve [AUC]) generally increased with increasing dose.

- For single dose studies, for doses > 10 mg/kg the t1/2 did not appear to increase with increasing pamrevlumab doses, based on available data with estimated mean t1/2 values of approximately 1 week.
- For multiple dose studies, the mean t1/2 following multiple doses (3 to 10 mg/kg) also increased from 102 to 135 hours.
    - The estimated t1/2 values for doses > 10 mg/kg did not appear to increase markedly with dose, based on available data (limited time points).

2.3.3 Safety

Key findings are summarized below from the Phase 1 and 2 studies involving more than 400 adults with diabetic kidney disease, idiopathic pulmonary fibrosis, and liver fibrosis due to hepatitis B or pancreatic cancer:

- Overall, pamrevlumab was well tolerated across the range of doses noted above, and there were no dose-limiting toxicities.
- Treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity and transient in duration.
- Infusion-related reactions have been mild-to-moderate and are considered an identified risk of pamrevlumab administration.
- TEAEs were considered typical of the subjects' underlying medical condition(s) and, in the placebo-controlled studies, were equally distributed between placebo and pamrevlumab treatment groups.
- No apparent pattern to TEAEs that occurred within 24 hours after infusions was observed.
- No apparent pattern for treatment-emergent serious adverse events (TESAEs) was observed during clinical testing.

2.3.4 Efficacy

Key efficacy findings are summarized below from the Phase 1 and 2 studies of CTGF inhibition by pamrevlumab in indications other than DMD.

2.3.4.1 Pancreatic Cancer

Biweekly doses of up to and including 45 mg/kg and weekly doses of 17.5 and

22.5 mg/kg were administered to subjects with previously untreated locally advanced or metastatic pancreatic adenocarcinoma. Increased exposure to pamrevlumab was associated with increased survival. There appears to be a relationship between survival and trough blood levels of pamrevlumab (Cmin). Notably Cmin >150 mcg/mL after the first dose of pamrevlumab (Day 15) was associated with significantly increased progression free survival and overall survival.

A maximal effect in survival benefit was achieved at dose levels of 25 to 45 mg/kg/2 weeks.

2.3.4.2 Idiopathic Pulmonary Fibrosis (IPF)

In subjects with IPF who completed 45 weeks of dosing with 15 or 30 mg/kg pamrevlumab, approximately 40% of subjects had stable or improved lung fibrosis by quantitative high

resolution CT imaging compared to baseline values with approximately 30% having improved pulmonary fibrosis.

Overall, subjects with stable or improved lung fibrosis also had stable or improved FVC (% predicted).

2.4 Risks and Benefits

Pamrevlumab has been generally well tolerated with most adverse events being typical of those expected for subjects with the underlying disease conditions.

Infusion-related reactions have been observed in some subjects treated with pamrevlumab. Across studies in other indications, infusion-related reactions have been mild-to-moderate did not result in discontinuation of treatment with pamrevlumab, and did not result in the use of prophylaxis for subsequent infusions.

The favorable experience with pamrevlumab to date does not exclude the possibility of more severe infusion reactions occurring in future subjects.

This is the first clinical study of pamrevlumab in DMD. There are currently no confirmed benefits to subjects with DMD treated with pamrevlumab. However, a potential benefit of treatment with pamrevlumab is indicated in preclinical models of DMD and previous clinical studies of pamrevlumab in other indications where CTGF is also associated with disease progression.

Dose regimens equal to or exceeding 35 mg/kg have been implemented in other indications in adult subjects. The objective of these studies was to inhibit bioactive CTGF, which is associated with disease progression in a number of indications. Please refer to the Investigator's Brochure for a comprehensive summary of efficacy, safety, and exposure data.

The current study will explore the clinical relevance of CTGF inhibition, as indicated in preclinical models, in DMD patients.

2.5 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Periods

Pamrevlumab is administered as an IV infusion at a dose of 35 mg/kg every two weeks for up to three years (Day 0 to Week 156). The dose, frequency and route of administration correspond with dose regimens that were well tolerated and possibly associated with efficacy in clinical studies in adults with IPF and pancreatic cancer. In both of these indications pamrevlumab was administered at doses that included the targeted dose regimen for the current study (35 mg/kg bodyweight) and greater (45 mg/kg bodyweight). These doses were not associated with dose limiting toxicity.

The overall objective of all of these studies, including the current study, is to provide a dose associated with clinically relevant CTGF blockade to impede progression of serious disease states. Body weight-related dosing and utilization of a dose no greater than the maximal dose used in adults are expected to ensure that systemic exposure in the targeted pediatric population will not exceed the systemic exposure achieved in adults.

PK assessments will be done during the course of the study and facilitate ongoing monitoring of exposure to pamrevlumab during the course of the study.

The planned treatment duration is no longer than total treatment periods achieved in previous studies with pamrevlumab.

The duration of treatment of the current study is also similar to the duration of other studies in DMD and is expected to provide sufficient basis to evaluate potential benefit in the targeted pediatric population with DMD.

2.6 Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents. Detailed information regarding study conduct is found in Sections 10, 11, 12, and 13.

2.7 Population to be Studied

Non-ambulatory adolescents and adults with DMD will be enrolled in this trial. A detailed inclusion/exclusion list is provided in Section 5.

3 OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is to estimate pamrevlumab's efficacy in non- ambulatory subjects with DMD.

3.2 Secondary Objectives

The following are the secondary objectives of this trial:

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

4 STUDY DESIGN

4.1 Endpoints and Assessments

4.1.1 Primary Endpoint

The primary endpoint is the annual change from baseline to Week 104 in percent predicted forced vital capacity (FVC) during treatment with pamrevlumab.

4.1.2 Secondary Endpoints

The following are the secondary endpoints:

- Change from baseline to Week 104 in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow
- Change in LVEF from baseline to Week 104
- Change from baseline to Week 104 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 104 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 104 in cardiac fibrosis score assessed by MRI
- Change from baseline to Week 104 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

4.1.3 Exploratory, Pharmacokinetic and Pharmacodynamic Outcome Measures

Exploratory outcome measures for this trial are:

- Pharmacokinetic (PK) profile of pamrevlumab (including Cmin, Cmax, AUCtau, and t1/2) [In the first 12 subjects to have PK/PD samples though Day 14]
    - In the overall population
    - In subjects 12 to 16 years of age, inclusive
    - In subjects older than 16 years
    - Comparison of PK profiles across age groups
- Plasma and urine CTGF
- Creatine kinase (CK)
- Circulating biomarkers
- Exploratory analyses on primary and secondary efficacy endpoints at week 156 will be conducted at the end of the study.

4.1.4 Safety Assessments

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

4.2 Trial Overview

This study will be an open-label, single arm study that will initially enroll approximately 22 subjects. Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for up to 156 weeks. An interim analysis will be conducted after at least 10 to 12 subjects have completed 1 year of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow) on a continuous basis.

Upon completion of treatment or premature discontinuation from the trial, subjects will be asked to return to the investigative site to complete final safety and efficacy assessments.

4.3 Study Treatment

4.3.1 Dose and Schedule

Each subject will receive pamrevlumab (35 mg/kg) intravenously every 2 weeks (q2w). See Section 6 for detailed information on study drug formulation, storage, and administration.

4.3.2 Rationale for Dose and Schedule

The pamrevlumab dose is based on results of a study in adult subjects with pancreatic cancer. In that study (Section 2.3.4.1), minimum pamrevlumab blood levels (Cmin)

≥150 mcg/mL were associated with increased median survival and 1 year survival compared to subjects with Cmin <150 mcg/mL. Given the apparent threshold effect for increased benefit when minimal pamrevlumab exposure is ≥150 mcg/mL and based on PK analysis using these data, the planned dose of 35 mg/kg administered every 2 weeks is projected to achieve this minimum exposure in the targeted DMD study population.

4.4 Concomitant Medications, Procedures and Nondrug Therapies

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy.

Investigational agents, and those that receive marketing authorization during this trial, or approved product for DMD (e.g. eteplirsen) are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

Concomitant medications (any prescription and/or over-the-counter [OTC] preparation) and procedures or nondrug therapies (e.g., physical therapy or acupuncture) used by a subject while participating in this clinical trial must be recorded from the Screening Visit through the End-of-Study Visit.

Questions regarding potential impact of concomitant medications on evaluability of subjects should be addressed to the attention of the FibroGen Medical Monitor.

4.4.1 Contraception

Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy of a partner must be reported (Section 8.3.6).

4.5 Safety Plan

An ongoing safety review is facilitated by the unblinded nature of the study. FibroGen will review safety data and will communicate the results of these reviews to investigators by email or teleconference on a regular basis. In addition, FibroGen will review safety experience with investigators during teleconferences that will be held at least quarterly and include the conclusions of the Data Monitoring Committee's (DMC) latest data review.

FibroGen will notify investigators immediately if a new safety risk is identified.

4.6 Data Monitoring Committee

A DMC will be utilized and will be composed of external experts. Composition and responsibilities of the DMC are defined in a separate DMC charter.

DMC responsibilities include review of safety data, and may include available pharmacokinetic data, and pulmonary function tests.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. At least one historical FVC % predicted value within 18 months of baseline
10. Left ventricular ejection fraction ≥45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Subjects currently receiving heart failure cardiac medications (e.g. angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /μL

16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. gamma glutamyl transferase (GGT) ≤3 x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after the last dose of study drug

5.2 Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 156 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 156 weeks
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

5.3 Subject Withdrawal

Subjects may withdraw from the study at any time.

The investigator may remove a subject from study treatment for the following reasons:

- Adverse events, which in the opinion of the Principal Investigator and/or FibroGen preclude further study drug dosing
- Nonadherence to protocol-defined procedures, in particular missing of 3 or more sequential study drug infusions
- Not available for safety assessments

Subjects who discontinue the study early should be strongly encouraged to complete the evaluations described in Section 7.1.3.

5.4 Replacement of Subjects

Subjects may be replaced in this study if a subject's participation is not terminated due to safety or tolerability issues and is replaced prior to completion of targeted recruitment into the study. Replacement decisions will be made between the sponsor and investigator on a case-by-case basis.

5.5 Study Termination

This trial can be terminated by the sponsor at any time for any reason.

6 STUDY DRUG/TREATMENT SUPPLY

6.1 FibroGen Investigational Product

Pamrevlumab is a fully human IgG1 kappa monoclonal antibody that binds to CTGF.

6.1.1 Formulation

Pamrevlumab is supplied in single-use glass vials containing 10 mL of a sterile, preservative-free solution. The solution is composed of 10 mg/mL pamrevlumab, 1.60 mg/mL l-histidine, 3.08 mg/mL l-histidine HCl, 8.01 mg/mL sodium chloride and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0. If different vial sizes or new formulations are introduced during the course of the study, updates to formulation, storage, etc. will be provided through an amendment to the Pharmacy Manual and investigative site staff training.

6.1.2 Storage

Vials of pamrevlumab must be stored refrigerated (2°C to 8°C), in a temperature- controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation.

6.1.3 Preparation of Dose for Administration

The dose of pamrevlumab (35 mg/kg) for the first infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken every 3 months thereafter. Pamrevlumab may be administered undiluted or, for convenience of infusion, may be diluted with 0.9% Sodium Chloride Injection according to the Dose Preparation Instructions in the Study Reference Investigational Product (IP) Manual.

Pamrevlumab will be administered as soon as possible after release from the site's pharmacy and within 24 hours of preparation. Pamrevlumab will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

6.1.4 Administration

Study Drug	Dose	Route	Infusion Rate	Schedule
Pamrevlumab	35 mg/kg	IV	Not to exceed 150 cc/hour	Every 2 weeks
DO NOT ADMINISTER PAMREVLUMAB AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.				

Subjects who weigh more than 117 kg will receive the maximum allowed dose of 4.1 g. For this study, the overall rate of infusion for the prepared study drug should not exceed 150 cc/hour. Adjustments may be made to further slow the rate of infusion (infusing less than 150 cc/hour) in accordance with the investigator's clinical judgement. Subjects should be carefully monitored for reaction during the first infusion with a physician available as needed. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation. The IV access should remain in place and be maintained per site procedures until the end of this post treatment observation period. If a subject has an infusion reaction, the infusion rate may be slowed or

temporarily stopped, depending on the severity of symptoms. If a subject experiences an infusion reaction and continues pamrevlumab dosing, a physician must be immediately available during subsequent infusions and observation periods until the subject does not have any infusion reaction for three sequential infusions.

Premedication, such as antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are not normally administered before infusions of pamrevlumab.

Premedication may be used for subjects who experience infusion reactions at the discretion of the investigator after discussion with the Medical Monitor.

Pamrevlumab will be administered in a hospital or ambulatory setting with adequate facilities for managing medical emergencies for at least three infusions to confirm the subject does not have an infusion reaction. The study site must have trained staff and medications for the treatment of acute reactions, including anaphylaxis, immediately available. There is no specific treatment for a pamrevlumab overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

FibroGen may consider the use of properly trained home health care staff to administer the pamrevlumab infusions in the future and corresponding study assessments during the conduct of the study, consistent with institutional regulations and policies.

7 ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

7.1 Study Procedures by Visit

All study procedures and assessments will be performed in accordance with the Schedule of Assessments presented in Section 16.

For all potential subjects, screening procedures required to determine subject eligibility will be performed within 28 days prior to Day 0 (first infusion of pamrevlumab).

Potential subjects may be re-screened if initial screening procedures lie outside the 28-day screening period prior to planned study entry.

Subject's eligibility for this study will be reviewed and approved by Sponsor's medical monitor prior to subject enrollment.

The following assessments are relevant to the assessment of efficacy: pulmonary function tests (FVC, mean inspiratory flow (MIF), peak expiratory flow), Brooke Upper Extremity Rating Scale, Performance of the Upper Limb, pinch strength, grip strength, cardiac MRI, and muscle MRI. Refer to the Study Reference Manual for details.

Approved windows for performing study assessments are defined in the following sections.

7.1.1 Screening Period (no earlier than Day -28)

Assessments to be conducted during the screening period are presented in Appendix 1.

Screening assessments may be completed over several visits during the screening period. It is recommended that the less invasive screening assessments be performed first upon completion of the signed Informed Consent and/or Assent Form [ICF] (demographics, medical history, blood draws, electrocardiogram [ECG], vital signs (includes body weight and height), physical exam, pulmonary function tests (PFTs), and then followed by the more rigorous screening assessments (i.e., muscle function tests, cardiac MRI).

A cardiac MRI performed within 3 months prior to Day 0 (start of dosing) is acceptable to confirm eligibility based on the LVEF study entry criterion and as baseline cardiac MRI. If an historic MRI is not available, a cardiac MRI must be performed during the Screening Period.

An upper arm muscle MRI is not required to determine subject eligibility at screening, but may be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Muscle and pulmonary function tests (PFTs) will be performed during the screening period. Muscle function and PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.

If the subject cannot perform adequately due to illness (e.g. sinusitis, etc.) then the PFTs should be delayed until the subject can reliably perform the assessment within the 28-day screening window.

In addition, an exploratory blood sample will be drawn for analysis of circulating biomarkers of fibrosis and specific muscle miRNAs (dystromirs) prior to first pamrevlumab infusion.

7.1.2 Dosing Period

The dosing period begins on the first day of dosing with study treatment (Day 0) and continues through Week 156. Subjects will receive study drug every 2 weeks.

The visit window for all dosing visits is ±2 days. Visits should be scheduled based on the previous visit, not the baseline visit.

Assessments and procedures to be performed during the dosing period are presented in Section 16.

Muscle or pulmonary function tests that cannot be performed or produce inadequate results according to test procedures during a specified visit should be performed by the next scheduled dosing visit.

Both cardiac and muscle MRIs may be performed within ±2 weeks of the specified visit.

Blood samples will be drawn for pharmacokinetic analysis according to the schedule in Appendix 5. Blood draws to be collected on non-dosing days may be collected within ±1 day as outlined in Appendix 5.

7.1.3 End of Treatment

Assessments and procedures to be conducted after the last dose of study drug are presented in Appendix 4.

The end of treatment cardiac and muscle MRIs may be performed any time from

Week 156/EOT to Week 158/EOS (End of Study) visit.

Subjects who complete 156 weeks of treatment will have their end of treatment assessments performed at the Week 156/EOT visit.

7.1.4 Early Withdrawal from Treatment and Safety Follow-up Period

Subjects who prematurely discontinue the study should be strongly encouraged to complete the final efficacy evaluations scheduled for Week 156/EOT as applicable, and the safety follow-up evaluations scheduled for the Week 158/EOS visit (4 weeks following the last dose).

7.1.5 Safety Follow-Up Period

For all subjects, the final safety assessments should be completed at the Week 158/EOS visit, 4 weeks (±7 days) after the last dose of pamrevlumab.

7.1.6 Missed Visits

Every attempt must be made to complete all study visits as outlined in the Schedules of Assessments. Missed infusions will not be replaced. If a subject misses a scheduled efficacy assessment, the assessment should be performed as soon after the missed visit as feasible and within the windows specified above.

7.1.7 Unscheduled Visits

Unscheduled Visit assessments may be required at the discretion of the investigator.

7.2 Assessments

Please refer to the Schedules of Assessments (Section 16) for the scope and timing of assessments. Please refer to the Laboratory Manual for details regarding laboratory sample collection and processing; and the Study Reference Manual for details regarding the conduct of functional tests and MRIs.

7.2.1 Pulmonary Function Tests

The following pulmonary function tests (PFTs) will be performed to assess changes in lung function: forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow rate (PEF; PEFR), forced expiratory volume in 1 second (FEV1), and peak cough flow (Mayer, 2015, Miller, 2005).

7.2.2 Muscle Strength and Functional Measurements

The following assessments will be performed to assess changes in upper extremity strength and function: Brooke Upper Extremity Rating Scale (Brooke Scale), Performance of the Upper Limb (PUL), Grip Test, and Pinch Strength Test.

7.2.3 Cardiac MRI

Cardiac MRIs will be performed as per Section 16 to assess changes in left ventricular ejection fraction (LVEF) and presence of late gadolinium enhancement (LGE), a marker for myocardial fibrosis.

7.2.4 Muscle MRI

An upper arm muscle MRI at screening, will be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Upper arm (bicep) muscle MRIs will be performed as per Section 16.

7.2.5 Quality of Life Questionnaire

Pediatrics Outcomes Data Collection Instrument (PODCI) Quality Outcome Questionnaire will be performed to assess if treatment with pamrevlumab improves quality of life.

7.2.6 Vital Signs and Physical Examinations

A physical examination will be performed at screening and baseline (Day 0), approximately every 12 weeks and at Week 156/EOT. Complete physical exams will be performed at screening, Week 48, Week 104, and Week 156/EOT. Other examinations may be disease-specific or problem-oriented examinations.

Vital signs (pulse, respiration, sitting blood pressure, and temperature) will be collected at screening and at all visits. During infusion visits, vital signs will be collected prior to start of each infusion, within 15 minutes of the end of each infusion, and within 15 minutes of the completion of the post-infusion observation period.

7.2.7 Laboratory Assessments

All laboratory tests of blood and/or urine specimens will be performed at a central laboratory or FibroGen, as appropriate. A Central Laboratory Manual with instructions on specimen

collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local clinical laboratories will be used to assess and facilitate the management of adverse events and to provide usual standard of care (including blood draws required prior to MRIs). Local clinical laboratory data will not be collected in the study database except for hematocrit values provided with imaging data.

7.2.7.1 Safety Assessments

Blood samples will be 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.

Safety labs will be drawn at the site's local lab prior to MRIs to ensure there is no contraindication to MRI. Hematocrit should be included in the local lab draw as these results are required to assess fibrosis and will be provided to the central imaging vendor along with the MRI scans. Details are included in the Imaging Manual.

7.2.7.2 Pharmacokinetics

Plasma concentrations of pamrevlumab will be determined on Day 0 pre-dose and within 1 hour post infusion, then on Days 2, 4, 7, 10, and 14. The Day 14 sample should be on the same day of, but prior to the start of the next infusion of study drug.

Day 2, 4, 7, and 10 PK assessments represent target days following the first dose; however, actual sample collection time of up to ±1 day of the target time is acceptable as

long as the actual time of dosing and actual time of each sample collection are recorded accurately.

At Weeks 26 and 52, trough pamrevlumab levels (Cmin) will be determined prior to study drug infusion.

PK samples will also be drawn within 60 minutes of infusion completion at Week 52.

7.2.7.3 Plasma and Urine CTGF

Plasma and urine samples will be analyzed for CTGF concentrations from samples taken as described in Appendix 5.

7.2.7.4 HAHA

Blood samples will be drawn for analysis of human anti-human antibody (HAHA) according to the schedule in Appendix 5.

7.2.7.5 Biomarkers

Blood samples will be drawn for analysis of biomarkers. The exact biomarkers will be based on current scientific knowledge regarding CTGF, pamrevlumab and DMD at the time the tests are performed. No genetic testing will be performed.

8 ASSESSMENT OF SAFETY

8.1 Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Section 16. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the Study Drug.

8.2 Definitions

8.2.1 Definition of an Adverse Event (AE)

For the purpose of this study, an AE is any untoward medical occurrence that occurred in the protocol-specified AE reporting period, and which does not necessarily have a causal relationship with the study drug. An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the

protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.3.1).

8.2.2 Definition of a Serious Adverse Event (SAE)

A serious adverse event is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.2.3 Definition of an Infusion Reaction

Infusion reactions are immunologic reactions to an infused protein, and are different from events resulting from the process of infusing the protein (e.g., infusion site bruise) and are different from adverse events due to the infused protein's intended or unintended pharmacologic effects.

8.2.3.1 Acute Infusion Reaction

An acute infusion reaction is one that meets both of the following criteria:

1. Occurs during or within 1 hour after infusion; and
2. Clinical manifestations consistent with:
    - IgE-mediated and non-IgE mediated hypersensitivity reactions, including but not limited to urticaria, skin rashes, angioedema, laryngeal edema, bronchospasm, gastrointestinal symptoms and hypotension; or
    - Cytokine release syndrome, including but not limited to fever, respiratory symptoms without the presence of wheezing, tremors, chills, flushing, pruritus, changes in blood pressure, dyspnea, chest discomfort, back pain, nausea, vomiting, diarrhea, and skin rashes.

8.2.3.2 Delayed Infusion Reaction

A delayed infusion reaction is one that meets both of the following criteria:

1. Occurs ≥1 hour after the infusion
2. Clinical manifestations as described above.

8.2.3.3 Reporting Possible and Confirmed Infusion Reactions

Both acute and delayed infusion reactions will be captured as AEs and also be reported to the medical monitor within 24 hours. See Study Reference Manual for additional details.

8.2.4 Special Situations

Certain safety events, called 'Special Situations' that occur in association with the study drug(s) include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving the medicinal product (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

Special Situations will be reported to the sponsor or designated vendor within 24 hours on a Medication Error report form. See Study Reference Manual for details.

8.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 4 weeks after the last dose of study drug, except for pregnancy reporting (Section 8.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5).

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever is possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff.

New indications for medications started during the AE reporting period (i.e., after informed consent is obtained until 4 weeks after the last dose of study drug) will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the Investigator to meet the specified criteria.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

8.3.3 Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 4.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild:** Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; ; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death:** Fatal AE.

8.3.4 Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- **Related:**
    - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re- occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- **Not Related:**
    - The event represents a pre-existing underlying disease that has not worsened on study
    - The event has the same characteristics of a known side-effect associated with a co-medication

- The event is an anticipated medical condition of anticipated severity for the study population
- The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5 Reporting Serious Adverse Events on the SAE Report Form

An SAE must be reported to the Sponsor and/or its designated safety management vendor within 24 hours of becoming aware of the SAE.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

The contact information for SAE reporting is as follows:

U.S. Toll-Free Fax Number: [redacted] Email: [redacted]

8.3.5.1 Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2 Deaths

The investigator will report the fatal or life-threatening event immediately to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to

4 weeks after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. Additionally, the site must complete the appropriate CRF page.

8.3.6 Pregnancies: Reporting and Follow-up of Subjects

The outcome of all pregnancies should be followed up and documented as described. Consent must be obtained from male subject's partner to collect information related to the pregnancy and outcome (and will be handled on a case-by-case basis with IRB/IEC approval). A Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

8.3.7 Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all laboratory results throughout the study in a timely manner, and determine whether any abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

This study tests the hypothesis of whether pamrevlumab can attenuate the annual decline from baseline to Week 104 in FVC in non-ambulatory DMD patients. A total of 22 subjects is planned to achieve 80% power to test the null hypothesis of change in percent predicted FVC of -5% against the alternative hypothesis, assuming a mean change of -2% and standard deviation of 5% based on 2-sided one sample t-test at 0.05 significance level. The hypotheses are:

H0: change in percent predicted FVC less than or equal to -5%

Ha: change in percent predicted FVC greater than -5%.

The primary efficacy endpoint will be met if the annual change in percent predicted FVC is greater than -5% at the end of the study (lower bound of 2-sided 95% confidence interval is greater than -5%).

9.2 Analysis Populations

9.2.1 Safety Population

The Safety Population will consist of all subjects who have received any dose of pamrevlumab. This population is also defined as the intent-to-treat (ITT) population.

9.2.2 Full Analysis Set Population

The Full Analysis Set Population (FAS) will consist of all subjects in the Safety Population who have at least one evaluable post-baseline FVC assessment.

9.3 Statistical Analysis

9.3.1 General Considerations

Descriptive summaries will be provided for all study parameters including baseline characteristics, safety, efficacy, pharmacokinetic and pharmacodynamic parameters. Continuous variables will be reported using number of subjects, mean, standard deviation or standard error, median, minimum, and maximum. In general, standard deviation is provided to describe the distribution of a parameter, such as baseline, safety, and PK/PD parameters; standard error is provided for statistical analyses of efficacy endpoints. Geometric mean will be included for PK/PD variables. Categorical variables will be reported by the frequency and percentage of subjects within each outcome category. Two-sided 95% confidence intervals will be presented for key efficacy parameters and two-sided 90% confidence intervals for PK/PD parameters. All statistical tests will be performed at α=0.05 level of significance, using two-sided tests, unless otherwise stated. Assessments as well as derived parameters will be presented in data listings for all subjects in the ITT/Safety Population.

9.3.2 Subject Enrollment and Disposition

The number of subjects in each study population as well as subject completion status and reasons for early discontinuation will be summarized.

9.3.3 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, and quality of life parameters.

9.4 Efficacy Analyses

Efficacy analyses will be based on the FAS population. Rules of handling missing data will be described in the Statistical Analysis Plan (SAP). Analyses based on observed data will be performed for sensitivity evaluation.

9.4.1 Primary Endpoint

The primary endpoint is the annual change from baseline to Week 104 in percent predicted FVC during treatment with pamrevlumab. The mean annual change in percent predicted FVC and the corresponding 2-sided 95% confidence interval will be presented. The primary efficacy endpoint will be met if the lower bound of 2-sided 95% confidence interval is greater than -5%.

9.4.2 Analyses of Other PFT Parameters

Changes from baseline to Week 104 in other PFT parameters will be estimated similarly; details of missing data handling will be described in the statistical analysis plan (SAP).

9.4.3 Analysis of PUL Parameters, Pinch and Grip Strength, Brooke Scale

Change from baseline to Week 104 in hand/arm function and strength will be analyzed. In order to evaluate overall effect, composite scores may be explored. Two-sided 95% confidence intervals will be presented.

9.4.4 Analysis of LVEF, Cardiac Fibrosis, and Muscle Fat and Fibrosis

Changes from baseline in LVEF, cardiac fibrosis, and muscle fat and fibrosis will be summarized descriptively based on available data at Week 104.

9.4.5 Analysis of PODCI Quality Outcome Data

Changes from baseline in modified PODCI scores of subjects will be summarized descriptively based on available data at each assessment time point.

9.4.6 Pharmacokinetic Analyses

Pamrevlumab concentrations and derived PK parameters (including Cmin, Cmax, AUCtau, and t1/2) will be summarized using descriptive statistics. Pharmacokinetic analysis will be performed using commercial software such as WinNonlin.

Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the

PK parameters (1) in the overall population, (2) in subjects 12 to 16 years of age, and

(3) in subjects older than 16 years. Comparison of PK parameters between the age groups will be performed. Trough values, measured at several time points during the course of the study, will be compared to determine steady state and accumulation.

9.4.7 Safety Analyses

Safety analyses will include summary of adverse events, prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs). In general, safety data will only be summarized descriptively and no inferential statistical procedures will be applied.

For data summarization, adverse events will be classified into standard terminology using a coding thesaurus (MedDRA), and reported by system organ class and preferred term.

Treatment-emergent adverse events will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Deaths, SAEs, and AEs leading to study or treatment discontinuation, and infusion reactions will be listed or tabulated separately.

Clinically significant changes from baseline in vital signs, laboratory tests, and ECG will be identified. Shift tables will summarize changes in selected laboratory measures.

All safety analyses will be performed based on the Safety Population.

9.5 Administrative Analyses

In this open-label exploratory study, safety will be monitored on an ongoing basis.

The DMC will review all safety data, which may include available pharmacokinetic data, and pulmonary function tests.

10 DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the International Conference on Harmonisation (ICH) E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IVRS [or IWRS], clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The investigator must also permit the U.S. FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the investigator is notified of an inspection pertaining to this study by the U.S. FDA or other applicable regulatory authorities, the investigator must notify FibroGen immediately.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents

11.2 Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

12 ETHICS

12.1 Ethical Considerations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

12.2 Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

12.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent (ICF) and/or Assent Form from the subject or written Informed Consent Form signed by the subject's legally authorized representative, as applicable. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be

a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

12.4 Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

13 DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs/eCRFs and resolved queries.

13.2 Data Collection, Handling, and Verification

All required data will either be entered onto CRFs/eCRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with a full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion, ensuring that all data is verifiable with source documents.

14 PUBLICATION POLICY

A detailed explanation of FibroGen's publication policy is described in the Clinical Trial Agreement.

15 REFERENCES

Au CG, Butler TL, Sherwood MC, Egan JR, North KN, Winlaw DS (2011) Increased connective tissue growth factor associated with cardiac fibrosis in the mdx mouse model of dystrophic cardiomyopathy. Int J Exp Pathol 92: (1):57-65

Bushby K, Finkel R, Birnkrant DJ, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 9: (1):77-93

Desguerre I, Mayer M, Leturcq F, Barbet JP, Gherardi RK, Christov C (2009) Endomysial fibrosis in Duchenne muscular dystrophy: a marker of poor outcome associated with macrophage alternative activation. J Neuropathol Exp Neurol 68: (7):762-773

Emery AE (1991) Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord 1: (1):19-29

Kharraz Y, Guerra J, Pessina P, Serrano AL, Munoz-Canoves P (2014) Understanding the process of fibrosis in Duchenne muscular dystrophy. Biomed Res Int 2014:965631

Mayer OH, Finkel RS, Rummey C, et al. (2015) Characterization of pulmonary function in Duchenne Muscular Dystrophy. Pediatr Pulmonol 50: (5):487-494

McKim DA, Katz SL, Barrowman N, Ni A, LeBlanc C (2012) Lung volume recruitment slows pulmonary function decline in Duchenne muscular dystrophy. Archives of Physical Medicine and Rehabilitation 93: (7):1117-1122

Miller MR, Hankinson J, Brusasco V, et al. (2005) Standardisation of spirometry. Eur Respir J 26: (2):319-338

Morales MG, Cabello-Verrugio C, Santander C, Cabrera D, Goldschmeding R, Brandan E (2011) CTGF/CCN-2 over-expression can directly induce features of skeletal muscle dystrophy. J Pathol 225: (4):490-501

Morales MG, Gutierrez J, Cabello-Verrugio C, et al. (2013) Reducing CTGF/CCN2 slows down mdx muscle dystrophy and improves cell therapy. Hum Mol Genet 22: (24):4938-4951

Pessina P, Cabrera D, Morales MG, et al. (2014) Novel and optimized strategies for inducing fibrosis in vivo: Focus on Duchenne Muscular Dystrophy. Skelet Muscle 4:7

Phillips MF, Quinlivan RC, Edwards RH, Calverley PM (2001) Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med 164: (12):2191-2194

Schram G, Fournier A, Leduc H, et al. (2013) All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 61: (9):948-954

Sun G, Haginoya K, Wu Y, et al. (2008) Connective tissue growth factor is overexpressed in muscles of human muscular dystrophy. J Neurol Sci 267: (1-2):48-56

Tandon A, Villa CR, Hor KN, et al. (2015) Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. J Am Heart Assoc 4: (4):e001338

Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH (2001) Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. Arch Dis Child 84: (6):521-524

Vial C, Zuniga LM, Cabello-Verrugio C, Canon P, Fadic R, Brandan E (2008) Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. Journal of Cellular Physiology 215: (2):410-421

16 APPENDICES

Appendix 1. Schedule of Assessments: Screening Period through Week 26

Assessment[a]	Screening Period (4 Weeks)	Treatment Period (Weeks)													
		Day 0	2	4	6	8	10	12	14	16	18	20	22	24	26
Informed Consent & Assent	X														
Inclusion/ Exclusion	X														
Demographics	X														
Medical History	X														
Clinical laboratory assessments[b,i]	X			X		X		X						X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X							X						X	
Electrocardiogram	X														
Physical Examination[e]	X	X						X						X	
Muscle function tests[f]	X	X						X						X	
Pulmonary function tests[g]	X	X						X						X	
Cardiac MRI[i]	X[i]														
Muscle MRI[i]	X[i]														
Specialty labs[h]		X	X												X
Pamrevlumab infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire		X													X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting BP, temperature) to be collected at every visit, and pre-infusion, within 15 minutes of completion, and within 15 minutes of completing observation period.
d. Weight and height (estimated from ulna length) to be measured at screening and every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at screening. Other exams may be disease specific or problem oriented.
f. Muscle function tests (MFT): Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test. MFTs will be performed during the screening period. MFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
g. Pulmonary function tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow. PFTs will be performed during the screening period. PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Baseline muscle MRI may be conducted during the screening period or up to Week 4 dosing visit. Local safety labs are required prior to the MRIs, and must include hematocrit.

Appendix 2. Schedule of Assessments: Week 28 through Week 58

Assessment[a]	Treatment Period (Weeks)													
	28	30	32	34	36	38	40	42	44	46	48	50	52	54,56, 58
Clinical laboratory assessments[b,i]					X						X			
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]					X						X			
Electrocardiogram													X	
Physical Examination[e]					X						X			
Muscle function tests[f]					X						X			
Pulmonary function tests[g]					X						X			
Cardiac MRI[i]													X	
Muscle MRI[i]													X	
Specialty labs[h]													X	
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire													X	

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured at screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 48. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs are required prior to the MRIs and must include hematocrit.

Appendix 3. Schedule of Assessments: Week 60 through Week 104

Assessment[a]	Treatment Period (Weeks)								
	60	62,64, 66,68,70	72	74,76, 78,80,82	84	86,88,90, 92,94	96	98,100, 102	104
Clinical laboratory assessments[b,i]	X		X		X		X		
Vital Signs[c]	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X		X		X		X		
Electrocardiogram									X
Physical Examination[e]	X		X		X				X
Muscle function tests[f]	X		X		X				X
Pulmonary function tests[g]	X		X		X				X
Cardiac MRI[i]									X
Muscle MRI[i]									X
Specialty labs[h]									X
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire									X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured in screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 104. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs required prior to the MRIs and must include hematocrit.

Appendix 4. Schedule of Assessments: Week 106 through Week 158/EOS

Assessment[a]	Treatment Period (Weeks)								EOT	Safety Follow-up
	106, 108, 110, 112, 114	116	118, 120, 122, 124, 126	128	130, 132, 134, 136, 138	140	142, 144, 146, 148, 150	152	154	156/ EOT	158/ EOS
Clinical laboratory assessments[b,j]		X		X		X		X			X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]		X		X		X		X			
Electrocardiogram										X	
Physical Examination[e]		X		X		X				X	
Muscle function tests[f]		X		X		X				X	
Pulmonary function tests[g]		X		X		X				X	
Cardiac MRI[i]										X	
Muscle MRI[i]										X	
Specialty labs[h]										X	X
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X		
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire										X	

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured in screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 156/EOT. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs required prior to the MRIs and must include hematocrit.

Appendix 5. Specialty Lab Schedule

		Treatment Period									Safety Follow-up
Sample	**Timepoint**	**Day 0**	**Day 2 ±1 day**	**Day 4 ±1 day**	**Day 7 ±1 day**	**Day 10±1 day**	**Week 2**	**Week 26**	**Week 52**	**Week 104, 156/EOT**	**Week 158/EOS (4 weeks after last dose)**
Pamrevlumab Pk[a]	Before infusion	X					X	X	X		
	Within 1 hour after infusion	X							X		
	Time point sample (no infusion)		X	X	X	X					
HAHA[b]	Predose (when applicable)	X									X
CTGF[c]	Predose (when applicable)	X								X	
Exploratory[d]	Predose (when applicable)	X							X	X	

Abbreviations: CTGF = connective tissue growth factor; ET = early termination; HAHA = human anti-human antibody; PK = pharmacokinetic

a. Approximately 1-2 mL of blood will be collected for each measurement of pamrevlumab PK.

b. Approximately 1 mL of blood will be collected for each measurement of HAHA.

c. Blood and urine samples will be collected. Approximately 1 mL of blood and 0.5 mL of urine will be collected for each measurement of CTGF.

d. Approximately 5 mL of blood will be collected for each exploratory sample.

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
PROTOCOL NUMBER:	FGCL-3019-079
PHASE:	2
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	126630
STUDY DRUG:	Pamrevlumab (FG-3019)
INDICATION:	Duchenne Muscular Dystrophy
FIBROGEN MEDICAL MONITOR:	[redacted] FibroGen, Inc. [redacted] Telephone: Mobile: E-mail Address:
ORIGINAL PROTOCOL:	16 June 2015
AMENDMENT 1.0:	31 August 2015
AMENDMENT 2.0:	06 May 2016
AMENDMENT 3.0:	09 December 2016
AMENDMENT 4.0:	10 July 2017
AMENDMENT 5.0:	14 November 2017
AMENDMENT 6.0:	14 November 2018 (Site Specific – Site [redacted] and [redacted])

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE

STUDY ACKNOWLEDGEMENT

Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy

FGCL-3019-079

Original: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

Amendment 3.0: 09 December 2016

Amendment 4.0: 10 July 2017

Amendment 5.0: 14 November 2017

Amendment 6.0: 14 November 2018 (Site Specific – Site [redacted] and [redacted])

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen's designee. Please retain the original for your study files.

CO FIRMATIO OF PROTOCOL APPROVAL

Original Protocol Date: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

mendment 3.0: 09 December 2016

Amendment 4.0: IO July 2017

Amendment 5.0: 14 ovember 2017

Amendment 6.0: 14 ovember 2018 (ite pecific- Site [redacted]an[redacted]

This protocol is approved by FibroGen.

[redacted]

26 Nov - 2018

Date

FibroGen, Inc.

AMENDMENT 6.0: KEY CHANGES FROM AMENDMENT 5.0

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Key Change	**Rationale**	**Sections Affected**
Extended treatment duration from 156 weeks to 208 weeks, with exploratory analyses at week 208.	This allows subjects continued access to treatment, and the collection of more data.	Synopsis (Study Design, Study Procedures, Treatments), 2.5, 4.2, 7.1.2, 7.1.3, 7.1.4, 7.1.5, 7.2.6, Appendices 4 and 5.
Medical Monitor has been changed from [redacted] to [redacted]	Medical Monitor has been changed from [redacted] to [redacted]	Title Page

PROTOCOL SYNOPSIS	
Study Title:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
Protocol Number:	FGCL-3019-079, Amendment 6.0
Investigational Product:	Pamrevlumab (FG-3019) (Recombinant fully human IgG_1 kappa monoclonal antibody to connective tissue growth factor)
Study Phase:	Phase 2
Target Population:	Non-ambulatory subjects with Duchenne muscular dystrophy (DMD)
Number of Subjects Planned:	Approximately 22 subjects will be enrolled; interim analysis may increase sample size to approximately 32
Study Centers Planned:	Approximately 10 centers

OBJECTIVES

Primary Objective

To estimate pamrevlumab's efficacy in non-ambulatory subjects with DMD

Secondary Objectives

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

ENDPOINTS/ASSESSMENTS

Efficacy

Primary Endpoint

- Annual change from baseline to Week 104 in percent predicted forced vital capacity (FVC) during treatment with pamrevlumab.

Secondary Endpoints

- Change from baseline to 104 weeks in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow

- Change in LVEF from baseline to Week 104
- Change from baseline to Week 104 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 104 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 104 in cardiac fibrosis score assessed by magnetic resonance imaging (MRI)
- Change from baseline to Week 104 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

Exploratory, Pharmacokinetics, Pharmacodynamics

- Pharmacokinetic (PK) profile of pamrevlumab (including C_{min}, C_{max}, AUC_{tau}, and $t_{1/2}$) [In the first 12 subjects to have PK/PD samples though Day 14]
  - In the overall population
  - In subjects 12 to 16 years of age, inclusive
  - In subjects older than 16 years
  - Comparison of PK profiles across age groups
- Plasma and urine connective tissue growth factor (CTGF)
- Creatine kinase (CK)
- Circulating biomarkers
- Exploratory analyses on primary and secondary efficacy endpoints at week 156 will be conducted at the end of the study.

Safety

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

STUDY DESIGN

This study is an open-label, single arm study which will initially enroll approximately 22 subjects. Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for up to 208 weeks. An interim analysis will be conducted after at least 10 to 12 subjects have completed 52 weeks of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow).

STUDY PROCEDURES

Details regarding study procedures are provided as follows:
Appendix 1: Screening Period through Week 26

Appendix 2: Week 28 through Week 58
Appendix 3: Week 60 through Week 104
Appendix 4: Week 106 through Week 210/EOS
Appendix 5: Specialty Lab Schedule

MAIN SELECTION CRITERIA

Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. At least one historical FVC % predicted value within 18 months of baseline
10. Left ventricular ejection fraction ≥45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Subjects currently receiving heart failure cardiac medications (e.g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation.
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /µL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤3x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after last dose of study drug.

Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 156 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 156 weeks
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

TREATMENTS

Pamrevlumab Dose, and Mode of Administration

Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for 208 weeks. The dose of pamrevlumab (35 mg/kg) for the first infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken approximately every 3 months thereafter.

Concomitant Medications/Therapies:

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy. Investigational agents, and those that receive marketing authorization, or approved product for DMD (e.g. eteplirsen) during this trial are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed. Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

STATISTICAL METHODS

A total of 22 subjects is planned to achieve 80% power to test the null hypothesis of change in percent predicted FVC of -5% against the alternative hypothesis, assuming a mean change of -2% and standard deviation of 5%, based on a 2-sided one sample t-test

at 0.05 significance level.

The primary efficacy endpoint will be met if the annual change in percent predicted FVC is above -5% after 104 weeks of treatment with pamrevlumab (lower bound of the 2-sided 95% confidence interval is above -5%).

An interim analysis will be conducted after at least 10 to 12 subjects have completed 1 year of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

The primary efficacy endpoint is the annual change from baseline to Week 104 in percent predicted FVC during treatment with pamrevlumab. The mean annual change in percent predicted FVC and the corresponding 2-sided 95% confidence interval will be presented.

Final analysis of the primary and secondary endpoints will be described in the statistical analysis plan. Details of the interim analysis will be described in an interim analysis plan.

Pamrevlumab concentrations and derived PK parameters will be tabulated and summarized using descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters. Attainment of steady-state will be investigated.

Safety analyses will include summary of adverse events (including treatment emergent AEs, treatment emergent serious AEs, deaths, and infusion-associated AEs), prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs), and physical exams.

Table of Contents

LIST OF APPENDICES

2 BACKGROUND

2.1 Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G1 (IgG) kappa monoclonal antibody to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role. These diseases include liver fibrosis due to hepatitis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne muscular dystrophy (DMD). Pamrevlumab (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. Pamrevlumab contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2 Duchenne Muscle Dystrophy

Duchenne muscular dystrophy (DMD) is usually inherited in an X-linked recessive fashion, but it can occur as a result of spontaneous mutation in boys from families without a known history of the condition. On the basis of some 40 studies including several million male births, incidence at birth of Duchenne muscular dystrophy is around 1:3300, and its prevalence in the population (in terms of the total male population) is around 1:16500 (Emery, 1991).

DMD is a result of mutations (mainly deletions) in the dystrophin gene (DMD; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration with loss of independent ambulation by the age of 13 years (Bushby, 2010).

In skeletal muscles of DMD patients constant myofiber breakdown results in persistent activation of myofibroblasts and altered production of extracellular matrix (ECM) resulting in extensive fibrosis. Muscle fibrosis is the only myo-pathologic parameter that significantly correlated with poor motor outcome as assessed by quadriceps muscle strength, manual muscle testing of upper and lower limbs, and age at ambulation loss (Desguerre, 2009).

Patients with DMD are generally wheelchair bound before they develop significant respiratory muscle weakness. Respiratory complications are the primary cause of morbidity and mortality in DMD as progressive respiratory muscle weakness leads to hypoventilation and/or recurrent atelectasis and pneumonia, secondary to decreased cough effectiveness (McKim, 2012).

After age 10 to 14, patients gradually begin to lose respiratory muscle function based on pulmonary function tests (PFTs) such as forced vital capacity (FVC). The median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001, Tangsrud, 2001).

Because of improvements in respiratory care, cardiac dysfunction is now a leading cause of morbidity and mortality in DMD patients (Schram, 2013). Progressive myocardial fibrosis, as detected by late gadolinium enhancement (LGE), is strongly correlated with the left ventricular ejection fraction (LVEF) decline in Duchenne muscular dystrophy patients. Longer steroid treatment duration is associated with a lower age-related increase in myocardial fibrosis burden (Tandon, 2015).

2.2.1 Relevance of Connective Tissue Growth Factor (CTGF) in DMD

Connective tissue growth factor (CTGF) is a nonstructural regulatory protein present in the extracellular matrix that has an important role in fibrosis. Skeletal muscle from DMD patients, dystrophic dogs, and mdx mice all show elevated levels of CTGF (Sun, 2008).

CTGF can reproduce or amplify the effects of TGFβ on fibrosis by inducing collagen type 1, α5 integrin, and fibronectin much more potently than TGFβ in fibroblasts (Kharraz, 2014).

Comparison of mdx mice with normal or genetically depleted levels of CTGF revealed that exercised mice with reduced CTGF developed less fibrosis and exhibited better muscle strength than mice with normal levels of CTGF (Morales, 2013). In culture, both myoblasts and myotubes were shown to express and secrete CTGF to the medium, and respond to the growth factor by increasing the extracellular matrix constituents, partially inhibiting myoblasts differentiation and inducing myoblasts dedifferentiation (Vial, 2008).

In DMD, the role of CTGF might extend well beyond replacement fibrosis secondary to loss of muscle fibers, since its overexpression in skeletal muscle could by itself induce a dystrophic phenotype (Morales, 2013).

A major feature of the hearts of DMD patients is cardiac fibrosis. Cardiac fibrosis is associated with increased CTGF expression in the mdx mouse heart. CTGF may be a key mediator of early and persistent fibrosis in dystrophic cardiomyopathy (Au, 2011).

CTGF is critically involved in several chronic fibro-degenerative diseases. Pamrevlumab treatment has been shown to positively the affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.

2.3 Summary of Relevant Findings from Nonclinical and Clinical Trials

Please refer to the most recent version of pamrevlumab Investigator's Brochure.

2.3.1 Nonclinical Studies

In DMD, the genetic loss of the cytoskeletal protein dystrophin results in muscle damage that, leads to progressive replacement of muscle with fibrotic and fat tissue. This progressive muscle damage can be recapitulated in the DMD mouse model (mdx), and accelerated by muscle usage (Pessina, 2014).

As was observed with genetic depletion of CTGF, pharmacologic inhibition of active CTGF in mdx mice by treatment with pamrevlumab resulted in reduced fibrosis and skeletal muscle damage, as well as improved preservation of skeletal muscle strength in isolated muscles. The pamrevlumab treated mdx mice were also subjected to a test of exercise endurance, in which they showed better performance than mdx mice injected with control IgG (Morales, 2013).

Pamrevlumab treatment of mdx mice was associated with decreased skeletal muscle damage and fibrosis, decreased collagen III and fibronectin expression, decreased plasma creatine kinase (CK) (Morales, 2013), and increased isometric force of skeletal muscle (Morales, 2011).

2.3.2 Pharmacokinetics

Key findings are summarized below from Phase 1 and 2 studies investigating the pharmacokinetics (PK) of pamrevlumab in subjects with diabetic kidney disease, idiopathic pulmonary fibrosis, liver fibrosis and pancreatic cancer:

- Pamrevlumab was administered over the dose range of 3 to 45 mg/kg every 2 weeks, every 3 weeks, and 17.5 to 22.5 mg/kg weekly.
- Pamrevlumab exposure (e.g., mean/median Cmax and Cmin, area under the curve [AUC]) generally increased with increasing dose.

- For single dose studies, for doses > 10 mg/kg the t1/2 did not appear to increase with increasing pamrevlumab doses, based on available data with estimated mean t1/2 values of approximately 1 week.
- For multiple dose studies, the mean t1/2 following multiple doses (3 to 10 mg/kg) also increased from 102 to 135 hours.
    - The estimated t1/2 values for doses > 10 mg/kg did not appear to increase markedly with dose, based on available data (limited time points).

2.3.3 Safety

Key findings are summarized below from the Phase 1 and 2 studies involving more than 400 adults with diabetic kidney disease, idiopathic pulmonary fibrosis, and liver fibrosis due to hepatitis B or pancreatic cancer:

- Overall, pamrevlumab was well tolerated across the range of doses noted above, and there were no dose-limiting toxicities.
- Treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity and transient in duration.
- Infusion-related reactions have been mild-to-moderate and are considered an identified risk of pamrevlumab administration.
- TEAEs were considered typical of the subjects' underlying medical condition(s) and, in the placebo-controlled studies, were equally distributed between placebo and pamrevlumab treatment groups.
- No apparent pattern to TEAEs that occurred within 24 hours after infusions was observed.
- No apparent pattern for treatment-emergent serious adverse events (TESAEs) was observed during clinical testing.

2.3.4 Efficacy

Key efficacy findings are summarized below from the Phase 1 and 2 studies of CTGF inhibition by pamrevlumab in indications other than DMD.

2.3.4.1 Pancreatic Cancer

Biweekly doses of up to and including 45 mg/kg and weekly doses of 17.5 and

22.5 mg/kg were administered to subjects with previously untreated locally advanced or metastatic pancreatic adenocarcinoma. Increased exposure to pamrevlumab was associated with increased survival. There appears to be a relationship between survival and trough blood levels of pamrevlumab (Cmin). Notably Cmin >150 mcg/mL after the first dose of pamrevlumab (Day 15) was associated with significantly increased progression free survival and overall survival.

A maximal effect in survival benefit was achieved at dose levels of 25 to 45 mg/kg/2 weeks.

2.3.4.2 Idiopathic Pulmonary Fibrosis (IPF)

In subjects with IPF who completed 45 weeks of dosing with 15 or 30 mg/kg pamrevlumab, approximately 40% of subjects had stable or improved lung fibrosis by quantitative high

resolution CT imaging compared to baseline values with approximately 30% having improved pulmonary fibrosis.

Overall, subjects with stable or improved lung fibrosis also had stable or improved FVC (% predicted).

2.4 Risks and Benefits

Pamrevlumab has been generally well tolerated with most adverse events being typical of those expected for subjects with the underlying disease conditions.

Infusion-related reactions have been observed in some subjects treated with pamrevlumab. Across studies in other indications, infusion-related reactions have been mild-to-moderate did not result in discontinuation of treatment with pamrevlumab, and did not result in the use of prophylaxis for subsequent infusions.

The favorable experience with pamrevlumab to date does not exclude the possibility of more severe infusion reactions occurring in future subjects.

This is the first clinical study of pamrevlumab in DMD. There are currently no confirmed benefits to subjects with DMD treated with pamrevlumab. However, a potential benefit of treatment with pamrevlumab is indicated in preclinical models of DMD and previous clinical studies of pamrevlumab in other indications where CTGF is also associated with disease progression.

Dose regimens equal to or exceeding 35 mg/kg have been implemented in other indications in adult subjects. The objective of these studies was to inhibit bioactive CTGF, which is associated with disease progression in a number of indications. Please refer to the Investigator's Brochure for a comprehensive summary of efficacy, safety, and exposure data.

The current study will explore the clinical relevance of CTGF inhibition, as indicated in preclinical models, in DMD patients.

2.5 Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Periods

Pamrevlumab is administered as an IV infusion at a dose of 35 mg/kg every two weeks (Day 0 to Week 208/EOT). The dose, frequency and route of administration correspond with dose regimens that were well tolerated and possibly associated with efficacy in clinical studies in adults with IPF and pancreatic cancer. In both of these indications pamrevlumab was administered at doses that included the targeted dose regimen for the current study (35 mg/kg bodyweight) and greater (45 mg/kg bodyweight). These doses were not associated with dose limiting toxicity.

The overall objective of all of these studies, including the current study, is to provide a dose associated with clinically relevant CTGF blockade to impede progression of serious disease states. Body weight-related dosing and utilization of a dose no greater than the maximal dose used in adults are expected to ensure that systemic exposure in the targeted pediatric population will not exceed the systemic exposure achieved in adults.

PK assessments will be done during the course of the study and facilitate ongoing monitoring of exposure to pamrevlumab during the course of the study.

The planned treatment duration is no longer than total treatment periods achieved in previous studies with pamrevlumab.

The duration of treatment of the current study is also similar to the duration of other studies in DMD and is expected to provide sufficient basis to evaluate potential benefit in the targeted pediatric population with DMD.

2.6 Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents. Detailed information regarding study conduct is found in Sections 10, 11, 12, and 13.

2.7 Population to be Studied

Non-ambulatory adolescents and adults with DMD will be enrolled in this trial. A detailed inclusion/exclusion list is provided in Section 5.

3 OBJECTIVES

3.1 Primary Objective

The primary objective of this trial is to estimate pamrevlumab's efficacy in non- ambulatory subjects with DMD.

3.2 Secondary Objectives

The following are the secondary objectives of this trial:

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

4 STUDY DESIGN

4.1 Endpoints and Assessments

4.1.1 Primary Endpoint

The primary endpoint is the annual change from baseline to Week 104 in percent predicted forced vital capacity (FVC) during treatment with pamrevlumab.

4.1.2 Secondary Endpoints

The following are the secondary endpoints:

- Change from baseline to Week 104 in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow
- Change in LVEF from baseline to Week 104
- Change from baseline to Week 104 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 104 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 104 in cardiac fibrosis score assessed by MRI
- Change from baseline to Week 104 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

4.1.3 Exploratory, Pharmacokinetic and Pharmacodynamic Outcome Measures

Exploratory outcome measures for this trial are:

- Pharmacokinetic (PK) profile of pamrevlumab (including Cmin, Cmax, AUCtau, and t1/2) [In the first 12 subjects to have PK/PD samples though Day 14]
    - In the overall population
    - In subjects 12 to 16 years of age, inclusive
    - In subjects older than 16 years
    - Comparison of PK profiles across age groups
- Plasma and urine CTGF
- Creatine kinase (CK)
- Circulating biomarkers
- Exploratory analyses on primary and secondary efficacy endpoints at week 156 will be conducted at the end of the study.

4.1.4 Safety Assessments

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

4.2 Trial Overview

This study will be an open-label, single arm study that will initially enroll approximately 22 subjects. Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for up to 208 weeks. An interim analysis will be conducted after at least 10 to 12 subjects have completed 1 year of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow) on a continuous basis.

Upon completion of treatment or premature discontinuation from the trial, subjects will be asked to return to the investigative site to complete final safety and efficacy assessments.

4.3 Study Treatment

4.3.1 Dose and Schedule

Each subject will receive pamrevlumab (35 mg/kg) intravenously every 2 weeks (q2w). See Section 6 for detailed information on study drug formulation, storage, and administration.

4.3.2 Rationale for Dose and Schedule

The pamrevlumab dose is based on results of a study in adult subjects with pancreatic cancer. In that study (Section 2.3.4.1), minimum pamrevlumab blood levels (Cmin)

≥150 mcg/mL were associated with increased median survival and 1 year survival compared to subjects with Cmin <150 mcg/mL. Given the apparent threshold effect for increased benefit when minimal pamrevlumab exposure is ≥150 mcg/mL and based on PK analysis using these data, the planned dose of 35 mg/kg administered every 2 weeks is projected to achieve this minimum exposure in the targeted DMD study population.

4.4 Concomitant Medications, Procedures and Nondrug Therapies

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy.

Investigational agents, and those that receive marketing authorization during this trial, or approved product for DMD (e.g. eteplirsen) are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

Concomitant medications (any prescription and/or over-the-counter [OTC] preparation) and procedures or nondrug therapies (e.g., physical therapy or acupuncture) used by a subject while participating in this clinical trial must be recorded from the Screening Visit through the End-of-Study Visit.

Questions regarding potential impact of concomitant medications on evaluability of subjects should be addressed to the attention of the FibroGen Medical Monitor.

4.4.1 Contraception

Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy of a partner must be reported (Section 8.3.6).

4.5 Safety Plan

An ongoing safety review is facilitated by the unblinded nature of the study. FibroGen will review safety data and will communicate the results of these reviews to investigators by email or teleconference on a regular basis. In addition, FibroGen will review safety experience with investigators during teleconferences that will be held at least quarterly and include the conclusions of the Data Monitoring Committee's (DMC) latest data review.

FibroGen will notify investigators immediately if a new safety risk is identified.

4.6 Data Monitoring Committee

A DMC will be utilized and will be composed of external experts. Composition and responsibilities of the DMC are defined in a separate DMC charter.

DMC responsibilities include review of safety data, and may include available pharmacokinetic data, and pulmonary function tests.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. At least one historical FVC % predicted value within 18 months of baseline
10. Left ventricular ejection fraction ≥45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Subjects currently receiving heart failure cardiac medications (e.g. angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /µL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. gamma glutamyl transferase (GGT) ≤3 x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after the last dose of study drug

5.2 Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 156 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 156 weeks
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

5.3 Subject Withdrawal

Subjects may withdraw from the study at any time.

The investigator may remove a subject from study treatment for the following reasons:

- Adverse events, which in the opinion of the Principal Investigator and/or FibroGen preclude further study drug dosing
- Nonadherence to protocol-defined procedures, in particular missing of 3 or more sequential study drug infusions
- Not available for safety assessments

Subjects who discontinue the study early should be strongly encouraged to complete the evaluations described in Section 7.1.3.

5.4 Replacement of Subjects

Subjects may be replaced in this study if a subject's participation is not terminated due to safety or tolerability issues and is replaced prior to completion of targeted recruitment into the study. Replacement decisions will be made between the sponsor and investigator on a case-by-case basis.

5.5 Study Termination

This trial can be terminated by the sponsor at any time for any reason.

6 STUDY DRUG/TREATMENT SUPPLY

6.1 FibroGen Investigational Product

Pamrevlumab is a fully human IgG1 kappa monoclonal antibody that binds to CTGF.

6.1.1 Formulation

Pamrevlumab is supplied in single-use glass vials containing 10 mL of a sterile, preservative-free solution. The solution is composed of 10 mg/mL pamrevlumab, 1.60 mg/mL l-histidine, 3.08 mg/mL l-histidine HCl, 8.01 mg/mL sodium chloride and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0. If different vial sizes or new formulations are introduced during the course of the study, updates to formulation, storage, etc. will be provided through an amendment to the Pharmacy Manual and investigative site staff training.

6.1.2 Storage

Vials of pamrevlumab must be stored refrigerated (2°C to 8°C), in a temperature- controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation.

6.1.3 Preparation of Dose for Administration

The dose of pamrevlumab (35 mg/kg) for the first infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken every 3 months thereafter. Pamrevlumab may be administered undiluted or, for convenience of infusion, may be diluted with 0.9% Sodium Chloride Injection according to the Dose Preparation Instructions in the Study Reference Investigational Product (IP) Manual.

Pamrevlumab will be administered as soon as possible after release from the site's pharmacy and within 24 hours of preparation. Pamrevlumab will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

6.1.4 Administration

Study Drug	Dose	Route	Infusion Rate	Schedule
Pamrevlumab	35 mg/kg	IV	Not to exceed 150 cc/hour	Every 2 weeks
DO NOT ADMINISTER PAMREVLUMAB AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.				

Subjects who weigh more than 117 kg will receive the maximum allowed dose of 4.1 g. For this study, the overall rate of infusion for the prepared study drug should not exceed 150 cc/hour. Adjustments may be made to further slow the rate of infusion (infusing less than 150 cc/hour) in accordance with the investigator's clinical judgement. Subjects should be carefully monitored for reaction during the first infusion with a physician available as needed. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation. The IV access should remain in place and be maintained per site procedures until the end of this post treatment observation period. If a subject has an infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences an infusion

reaction and continues pamrevlumab dosing, a physician must be immediately available during subsequent infusions and observation periods until the subject does not have any infusion reaction for three sequential infusions.

Premedication, such as antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are not normally administered before infusions of pamrevlumab.

Premedication may be used for subjects who experience infusion reactions at the discretion of the investigator after discussion with the Medical Monitor.

Pamrevlumab will be administered in a hospital or ambulatory setting with adequate facilities for managing medical emergencies for at least three infusions to confirm the subject does not have an infusion reaction. The study site must have trained staff and medications for the treatment of acute reactions, including anaphylaxis, immediately available. There is no specific treatment for a pamrevlumab overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

FibroGen may consider the use of properly trained home health care staff to administer the pamrevlumab infusions in the future and corresponding study assessments during the conduct of the study, consistent with institutional regulations and policies.

7 ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

7.1 Study Procedures by Visit

All study procedures and assessments will be performed in accordance with the Schedule of Assessments presented in Section 16.

For all potential subjects, screening procedures required to determine subject eligibility will be performed within 28 days prior to Day 0 (first infusion of pamrevlumab).

Potential subjects may be re-screened if initial screening procedures lie outside the 28-day screening period prior to planned study entry.

Subject's eligibility for this study will be reviewed and approved by Sponsor's medical monitor prior to subject enrollment.

The following assessments are relevant to the assessment of efficacy: pulmonary function tests (FVC, mean inspiratory flow (MIF), peak expiratory flow), Brooke Upper Extremity Rating Scale, Performance of the Upper Limb, pinch strength, grip strength, cardiac MRI, and muscle MRI. Refer to the Study Reference Manual for details.

Approved windows for performing study assessments are defined in the following sections.

7.1.1 Screening Period (no earlier than Day -28)

Assessments to be conducted during the screening period are presented in Appendix 1.

Screening assessments may be completed over several visits during the screening period. It is recommended that the less invasive screening assessments be performed first upon completion of the signed Informed Consent and/or Assent Form [ICF] (demographics, medical history, blood draws, electrocardiogram [ECG], vital signs (includes body weight and height), physical exam, pulmonary function tests (PFTs), and then followed by the more rigorous screening assessments (i.e., muscle function tests, cardiac MRI).

A cardiac MRI performed within 3 months prior to Day 0 (start of dosing) is acceptable to confirm eligibility based on the LVEF study entry criterion and as baseline cardiac MRI. If an historic MRI is not available, a cardiac MRI must be performed during the Screening Period.

An upper arm muscle MRI is not required to determine subject eligibility at screening, but may be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Muscle and pulmonary function tests (PFTs) will be performed during the screening period. Muscle function and PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.

If the subject cannot perform adequately due to illness (e.g. sinusitis, etc.) then the PFTs should be delayed until the subject can reliably perform the assessment within the 28-day screening window.

In addition, an exploratory blood sample will be drawn for analysis of circulating biomarkers of fibrosis and specific muscle miRNAs (dystromirs) prior to first pamrevlumab infusion.

7.1.2 Dosing Period

The dosing period begins on the first day of dosing with study treatment (Day 0) and continues through Week 208. Subjects will receive study drug every 2 weeks.

The visit window for all dosing visits is ±2 days. Visits should be scheduled based on the previous visit, not the baseline visit.

Assessments and procedures to be performed during the dosing period are presented in Section 16.

Muscle or pulmonary function tests that cannot be performed or produce inadequate results according to test procedures during a specified visit should be performed by the next scheduled dosing visit.

Both cardiac and muscle MRIs may be performed within ±2 weeks of the specified visit.

Blood samples will be drawn for pharmacokinetic analysis according to the schedule in Appendix 5. Blood draws to be collected on non-dosing days may be collected within ±1 day as outlined in Appendix 5.

7.1.3 End of Treatment

Assessments and procedures to be conducted after the last dose of study drug are presented in Appendix 4.

The end of treatment cardiac and muscle MRIs may be performed any time from

Week 208/EOT to Week 210/EOS (End of Study) visit.

Subjects who complete 208 weeks of treatment will have their end of treatment assessments performed at the Week 208/EOT visit.

7.1.4 Early Withdrawal from Treatment and Safety Follow-up Period

Subjects who prematurely discontinue the study should be strongly encouraged to complete the final efficacy evaluations scheduled for Week 208/EOT as applicable, and the safety follow-up evaluations scheduled for the Week 210/EOS visit (4 weeks following the last dose).

7.1.5 Safety Follow-Up Period

For all subjects, the final safety assessments should be completed at the Week 210/EOS visit, 4 weeks (±7 days) after the last dose of pamrevlumab.

7.1.6 Missed Visits

Every attempt must be made to complete all study visits as outlined in the Schedules of Assessments. Missed infusions will not be replaced. If a subject misses a scheduled efficacy assessment, the assessment should be performed as soon after the missed visit as feasible and within the windows specified above.

7.1.7 Unscheduled Visits

Unscheduled Visit assessments may be required at the discretion of the investigator.

7.2 Assessments

Please refer to the Schedules of Assessments (Section 16) for the scope and timing of assessments. Please refer to the Laboratory Manual for details regarding laboratory sample collection and processing; and the Study Reference Manual for details regarding the conduct of functional tests and MRIs.

7.2.1 Pulmonary Function Tests

The following pulmonary function tests (PFTs) will be performed to assess changes in lung function: forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow rate (PEF; PEFR), forced expiratory volume in 1 second (FEV1), and peak cough flow (Mayer, 2015, Miller, 2005).

7.2.2 Muscle Strength and Functional Measurements

The following assessments will be performed to assess changes in upper extremity strength and function: Brooke Upper Extremity Rating Scale (Brooke Scale), Performance of the Upper Limb (PUL), Grip Test, and Pinch Strength Test.

7.2.3 Cardiac MRI

Cardiac MRIs will be performed as per Section 16 to assess changes in left ventricular ejection fraction (LVEF) and presence of late gadolinium enhancement (LGE), a marker for myocardial fibrosis.

7.2.4 Muscle MRI

An upper arm muscle MRI at screening, will be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Upper arm (bicep) muscle MRIs will be performed as per Section 16.

7.2.5 Quality of Life Questionnaire

Pediatrics Outcomes Data Collection Instrument (PODCI) Quality Outcome Questionnaire will be performed to assess if treatment with pamrevlumab improves quality of life.

7.2.6 Vital Signs and Physical Examinations

A physical examination will be performed at screening and baseline (Day 0), approximately every 12 weeks and at Week 208/EOT. Complete physical exams will be performed at screening, Week 48, Week 104, Week 156, and Week 208/ EOT. Other examinations may be disease-specific or problem-oriented examinations.

Vital signs (pulse, respiration, sitting blood pressure, and temperature) will be collected at screening and at all visits. During infusion visits, vital signs will be collected prior to start of each infusion, within 15 minutes of the end of each infusion, and within 15 minutes of the completion of the post-infusion observation period.

7.2.7 Laboratory Assessments

All laboratory tests of blood and/or urine specimens will be performed at a central laboratory or FibroGen, as appropriate. A Central Laboratory Manual with instructions on specimen

collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local clinical laboratories will be used to assess and facilitate the management of adverse events and to provide usual standard of care (including blood draws required prior to MRIs). Local clinical laboratory data will not be collected in the study database except for hematocrit values provided with imaging data.

7.2.7.1 Safety Assessments

Blood samples will be 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.

Safety labs will be drawn at the site's local lab prior to MRIs to ensure there is no contraindication to MRI. Hematocrit should be included in the local lab draw as these results are required to assess fibrosis and will be provided to the central imaging vendor along with the MRI scans. Details are included in the Imaging Manual.

7.2.7.2 Pharmacokinetics

Plasma concentrations of pamrevlumab will be determined on Day 0 pre-dose and within 1 hour post infusion, then on Days 2, 4, 7, 10, and 14. The Day 14 sample should be on the same day of, but prior to the start of the next infusion of study drug.

Day 2, 4, 7, and 10 PK assessments represent target days following the first dose; however, actual sample collection time of up to ±1 day of the target time is acceptable as

long as the actual time of dosing and actual time of each sample collection are recorded accurately.

At Weeks 26 and 52, trough pamrevlumab levels (Cmin) will be determined prior to study drug infusion.

PK samples will also be drawn within 60 minutes of infusion completion at Week 52.

7.2.7.3 Plasma and Urine CTGF

Plasma and urine samples will be analyzed for CTGF concentrations from samples taken as described in Appendix 5.

7.2.7.4 HAHA

Blood samples will be drawn for analysis of human anti-human antibody (HAHA) according to the schedule in Appendix 5.

7.2.7.5 Biomarkers

Blood samples will be drawn for analysis of biomarkers. The exact biomarkers will be based on current scientific knowledge regarding CTGF, pamrevlumab and DMD at the time the tests are performed. No genetic testing will be performed.

8 ASSESSMENT OF SAFETY

8.1 Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Section 16. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the Study Drug.

8.2 Definitions

8.2.1 Definition of an Adverse Event (AE)

For the purpose of this study, an AE is any untoward medical occurrence that occurred in the protocol-specified AE reporting period, and which does not necessarily have a causal relationship with the study drug. An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the

protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.3.1).

8.2.2 Definition of a Serious Adverse Event (SAE)

A serious adverse event is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.2.3 Definition of an Infusion Reaction

Infusion reactions are immunologic reactions to an infused protein, and are different from events resulting from the process of infusing the protein (e.g., infusion site bruise) and are different from adverse events due to the infused protein's intended or unintended pharmacologic effects.

8.2.3.1 Acute Infusion Reaction

An acute infusion reaction is one that meets both of the following criteria:

1. Occurs during or within 1 hour after infusion; and
2. Clinical manifestations consistent with:
    - IgE-mediated and non-IgE mediated hypersensitivity reactions, including but not limited to urticaria, skin rashes, angioedema, laryngeal edema, bronchospasm, gastrointestinal symptoms and hypotension; or
    - Cytokine release syndrome, including but not limited to fever, respiratory symptoms without the presence of wheezing, tremors, chills, flushing, pruritus, changes in blood pressure, dyspnea, chest discomfort, back pain, nausea, vomiting, diarrhea, and skin rashes.

8.2.3.2 Delayed Infusion Reaction

A delayed infusion reaction is one that meets both of the following criteria:

1. Occurs ≥1 hour after the infusion
2. Clinical manifestations as described above.

8.2.3.3 Reporting Possible and Confirmed Infusion Reactions

Both acute and delayed infusion reactions will be captured as AEs and also be reported to the medical monitor within 24 hours. See Study Reference Manual for additional details.

8.2.4 Special Situations

Certain safety events, called 'Special Situations' that occur in association with the study drug(s) include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving the medicinal product (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

Special Situations will be reported to the sponsor or designated vendor within 24 hours on a Medication Error report form. See Study Reference Manual for details.

8.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 4 weeks after the last dose of study drug, except for pregnancy reporting (Section 8.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5).

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever is possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff.

New indications for medications started during the AE reporting period (i.e., after informed consent is obtained until 4 weeks after the last dose of study drug) will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the Investigator to meet the specified criteria.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

8.3.3 Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 4.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild:** Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; ; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- Grade 5, Death: Fatal AE.

8.3.4 Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- Related:
    - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re- occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- Not Related:
    - The event represents a pre-existing underlying disease that has not worsened on study
    - The event has the same characteristics of a known side-effect associated with a co-medication

- The event is an anticipated medical condition of anticipated severity for the study population
- The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5 Reporting Serious Adverse Events on the SAE Report Form

An SAE must be reported to the Sponsor and/or its designated safety management vendor within 24 hours of becoming aware of the SAE.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

The contact information for SAE reporting is as follows:

U.S. Toll-Free Fax Number: [redacted] Email: [redacted]

8.3.5.1 Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2 Deaths

The investigator will report the fatal or life-threatening event immediately to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to

4 weeks after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. Additionally, the site must complete the appropriate CRF page.

8.3.6 Pregnancies: Reporting and Follow-up of Subjects

The outcome of all pregnancies should be followed up and documented as described. Consent must be obtained from male subject's partner to collect information related to the pregnancy and outcome (and will be handled on a case-by-case basis with IRB/IEC approval). A Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

8.3.7 Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all laboratory results throughout the study in a timely manner, and determine whether any abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

9 STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

This study tests the hypothesis of whether pamrevlumab can attenuate the annual decline from baseline to Week 104 in FVC in non-ambulatory DMD patients. A total of 22 subjects is planned to achieve 80% power to test the null hypothesis of change in percent predicted FVC of -5% against the alternative hypothesis, assuming a mean change of -2% and standard deviation of 5% based on 2-sided one sample t-test at 0.05 significance level. The hypotheses are:

H0: change in percent predicted FVC less than or equal to -5%

Ha: change in percent predicted FVC greater than -5%.

The primary efficacy endpoint will be met if the annual change in percent predicted FVC is greater than -5% at the end of the study (lower bound of 2-sided 95% confidence interval is greater than -5%).

9.2 Analysis Populations

9.2.1 Safety Population

The Safety Population will consist of all subjects who have received any dose of pamrevlumab. This population is also defined as the intent-to-treat (ITT) population.

9.2.2 Full Analysis Set Population

The Full Analysis Set Population (FAS) will consist of all subjects in the Safety Population who have at least one evaluable post-baseline FVC assessment.

9.3 Statistical Analysis

9.3.1 General Considerations

Descriptive summaries will be provided for all study parameters including baseline characteristics, safety, efficacy, pharmacokinetic and pharmacodynamic parameters. Continuous variables will be reported using number of subjects, mean, standard deviation or standard error, median, minimum, and maximum. In general, standard deviation is provided to describe the distribution of a parameter, such as baseline, safety, and PK/PD parameters; standard error is provided for statistical analyses of efficacy endpoints. Geometric mean will be included for PK/PD variables. Categorical variables will be reported by the frequency and percentage of subjects within each outcome category. Two-sided 95% confidence intervals will be presented for key efficacy parameters and two-sided 90% confidence intervals for PK/PD parameters. All statistical tests will be performed at α=0.05 level of significance, using two-sided tests, unless otherwise stated. Assessments as well as derived parameters will be presented in data listings for all subjects in the ITT/Safety Population.

9.3.2 Subject Enrollment and Disposition

The number of subjects in each study population as well as subject completion status and reasons for early discontinuation will be summarized.

9.3.3 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, and quality of life parameters.

9.4 Efficacy Analyses

Efficacy analyses will be based on the FAS population. Rules of handling missing data will be described in the Statistical Analysis Plan (SAP). Analyses based on observed data will be performed for sensitivity evaluation.

9.4.1 Primary Endpoint

The primary endpoint is the annual change from baseline to Week 104 in percent predicted FVC during treatment with pamrevlumab. The mean annual change in percent predicted FVC and the corresponding 2-sided 95% confidence interval will be presented. The primary efficacy endpoint will be met if the lower bound of 2-sided 95% confidence interval is greater than -5%.

9.4.2 Analyses of Other PFT Parameters

Changes from baseline to Week 104 in other PFT parameters will be estimated similarly; details of missing data handling will be described in the statistical analysis plan (SAP).

9.4.3 Analysis of PUL Parameters, Pinch and Grip Strength, Brooke Scale

Change from baseline to Week 104 in hand/arm function and strength will be analyzed. In order to evaluate overall effect, composite scores may be explored. Two-sided 95% confidence intervals will be presented.

9.4.4 Analysis of LVEF, Cardiac Fibrosis, and Muscle Fat and Fibrosis

Changes from baseline in LVEF, cardiac fibrosis, and muscle fat and fibrosis will be summarized descriptively based on available data at Week 104.

9.4.5 Analysis of PODCI Quality Outcome Data

Changes from baseline in modified PODCI scores of subjects will be summarized descriptively based on available data at each assessment time point.

9.4.6 Pharmacokinetic Analyses

Pamrevlumab concentrations and derived PK parameters (including Cmin, Cmax, AUCtau, and t1/2) will be summarized using descriptive statistics. Pharmacokinetic analysis will be performed using commercial software such as WinNonlin.

Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the

PK parameters (1) in the overall population, (2) in subjects 12 to 16 years of age, and

(3) in subjects older than 16 years. Comparison of PK parameters between the age groups will be performed. Trough values, measured at several time points during the course of the study, will be compared to determine steady state and accumulation.

9.4.7 Safety Analyses

Safety analyses will include summary of adverse events, prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs). In general, safety data will only be summarized descriptively and no inferential statistical procedures will be applied.

For data summarization, adverse events will be classified into standard terminology using a coding thesaurus (MedDRA), and reported by system organ class and preferred term.

Treatment-emergent adverse events will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Deaths, SAEs, and AEs leading to study or treatment discontinuation, and infusion reactions will be listed or tabulated separately.

Clinically significant changes from baseline in vital signs, laboratory tests, and ECG will be identified. Shift tables will summarize changes in selected laboratory measures.

All safety analyses will be performed based on the Safety Population.

9.5 Administrative Analyses

In this open-label exploratory study, safety will be monitored on an ongoing basis.

The DMC will review all safety data, which may include available pharmacokinetic data, and pulmonary function tests.

10 DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the International Conference on Harmonisation (ICH) E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IVRS [or IWRS], clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The investigator must also permit the U.S. FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the investigator is notified of an inspection pertaining to this study by the U.S. FDA or other applicable regulatory authorities, the investigator must notify FibroGen immediately.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents

11.2 Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

12 ETHICS

12.1 Ethical Considerations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

12.2 Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

12.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent (ICF) and/or Assent Form from the subject or written Informed Consent Form signed by the subject's legally authorized representative, as applicable. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be

a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

12.4 Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

13 DATA HANDLING AND RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs/eCRFs and resolved queries.

13.2 Data Collection, Handling, and Verification

All required data will either be entered onto CRFs/eCRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with a full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion, ensuring that all data is verifiable with source documents.

14 PUBLICATION POLICY

A detailed explanation of FibroGen's publication policy is described in the Clinical Trial Agreement.

15 REFERENCES

Au CG, Butler TL, Sherwood MC, Egan JR, North KN, Winlaw DS (2011) Increased connective tissue growth factor associated with cardiac fibrosis in the mdx mouse model of dystrophic cardiomyopathy. Int J Exp Pathol 92: (1):57-65

Bushby K, Finkel R, Birnkrant DJ, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 9: (1):77-93

Desguerre I, Mayer M, Leturcq F, Barbet JP, Gherardi RK, Christov C (2009) Endomysial fibrosis in Duchenne muscular dystrophy: a marker of poor outcome associated with macrophage alternative activation. J Neuropathol Exp Neurol 68: (7):762-773

Emery AE (1991) Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord 1: (1):19-29

Kharraz Y, Guerra J, Pessina P, Serrano AL, Munoz-Canoves P (2014) Understanding the process of fibrosis in Duchenne muscular dystrophy. Biomed Res Int 2014:965631

Mayer OH, Finkel RS, Rummey C, et al. (2015) Characterization of pulmonary function in Duchenne Muscular Dystrophy. Pediatr Pulmonol 50: (5):487-494

McKim DA, Katz SL, Barrowman N, Ni A, LeBlanc C (2012) Lung volume recruitment slows pulmonary function decline in Duchenne muscular dystrophy. Archives of Physical Medicine and Rehabilitation 93: (7):1117-1122

Miller MR, Hankinson J, Brusasco V, et al. (2005) Standardisation of spirometry. Eur Respir J 26: (2):319-338

Morales MG, Cabello-Verrugio C, Santander C, Cabrera D, Goldschmeding R, Brandan E (2011) CTGF/CCN-2 over-expression can directly induce features of skeletal muscle dystrophy. J Pathol 225: (4):490-501

Morales MG, Gutierrez J, Cabello-Verrugio C, et al. (2013) Reducing CTGF/CCN2 slows down mdx muscle dystrophy and improves cell therapy. Hum Mol Genet 22: (24):4938-4951

Pessina P, Cabrera D, Morales MG, et al. (2014) Novel and optimized strategies for inducing fibrosis in vivo: Focus on Duchenne Muscular Dystrophy. Skelet Muscle 4:7

Phillips MF, Quinlivan RC, Edwards RH, Calverley PM (2001) Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med 164: (12):2191-2194

Schram G, Fournier A, Leduc H, et al. (2013) All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 61: (9):948-954

Sun G, Haginoya K, Wu Y, et al. (2008) Connective tissue growth factor is overexpressed in muscles of human muscular dystrophy. J Neurol Sci 267: (1-2):48-56

Tandon A, Villa CR, Hor KN, et al. (2015) Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. J Am Heart Assoc 4: (4):e001338

Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH (2001) Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. Arch Dis Child 84: (6):521-524

Vial C, Zuniga LM, Cabello-Verrugio C, Canon P, Fadic R, Brandan E (2008) Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. Journal of Cellular Physiology 215: (2):410-421

16 APPENDICES

Appendix 1. Schedule of Assessments: Screening Period through Week 26

Assessment[a]	Screening Period (4 Weeks)	Treatment Period (Weeks)													
		Day 0	2	4	6	8	10	12	14	16	18	20	22	24	26
Informed Consent & Assent	X														
Inclusion/ Exclusion	X														
Demographics	X														
Medical History	X														
Clinical laboratory assessments[b,i]	X			X		X		X						X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X							X						X	
Electrocardiogram	X														
Physical Examination[e]	X	X						X						X	
Muscle function tests[f]	X	X						X						X	
Pulmonary function tests[g]	X	X						X						X	
Cardiac MRI[i]	X[i]														
Muscle MRI[i]	X[i]														
Specialty labs[h]		X	X												X
Pamrevlumab infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire		X													X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting BP, temperature) to be collected at every visit, and pre-infusion, within 15 minutes of completion, and within 15 minutes of completing observation period.
d. Weight and height (estimated from ulna length) to be measured at screening and every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at screening. Other exams may be disease specific or problem oriented.
f. Muscle function tests (MFT): Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test. MFTs will be performed during the screening period. MFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
g. Pulmonary function tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow. PFTs will be performed during the screening period. PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Baseline muscle MRI may be conducted during the screening period or up to Week 4 dosing visit. Local safety labs are required prior to the MRIs, and must include hematocrit.

Appendix 2. Schedule of Assessments: Week 28 through Week 58

Assessment[a]	Treatment Period (Weeks)													
	28	30	32	34	36	38	40	42	44	46	48	50	52	54,56, 58
Clinical laboratory assessments[b,i]					X						X			
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]					X						X			
Electrocardiogram													X	
Physical Examination[e]					X						X			
Muscle function tests[f]					X						X			
Pulmonary function tests[g]					X						X			
Cardiac MRI[i]													X	
Muscle MRI[i]													X	
Specialty labs[h]													X	
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire													X	

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured at screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 48. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs are required prior to the MRIs and must include hematocrit.

Appendix 3. Schedule of Assessments: Week 60 through Week 104

Assessment[a]	Treatment Period (Weeks)								
	60	62,64, 66,68,70	72	74,76, 78,80,82	84	86,88,90, 92,94	96	98,100, 102	104
Clinical laboratory assessments[b,i]	X		X		X		X		
Vital Signs[c]	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X		X		X		X		
Electrocardiogram									X
Physical Examination[e]	X		X		X				X
Muscle function tests[f]	X		X		X				X
Pulmonary function tests[g]	X		X		X				X
Cardiac MRI[i]									X
Muscle MRI[i]									X
Specialty labs[h]									X
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire									X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured in screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 104. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs required prior to the MRIs and must include hematocrit.

Appendix 4. Schedule of Assessments: Week 106 through Week 210/EOS

Assessment[a]	Treatment Period (Weeks)										Safety Follow-up
	106, 108, 110, 112, 114	116	118, 120, 122, 124, 126	128	130, 132, 134, 136, 138	140	142, 144, 146, 148, 150	152	154	156	210/ EOS
	158, 160, 162, 164, 166	168	170, 172, 174, 176, 178	180	182, 184, 186, 188, 190	190	192, 194, 196, 198, 200	204	206	208/EOT	
Clinical laboratory assessments[b,j]		X		X		X		X			X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]		X		X		X		X			
Electrocardiogram										X	
Physical Examination[e]		X		X		X				X	
Muscle function tests[f]		X		X		X				X	
Pulmonary function tests[g]		X		X		X				X	
Cardiac MRI[i]										X	
Muscle MRI[i]										X	
Specialty labs[h]										X	X
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X	X[j]	
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire										X	

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured in screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 208/EOT. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.

g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs required prior to the MRIs and must include hematocrit.
j. Pamrevlumab infusion is administered at Week 156, but is NOT to be administered at week 208/EOT.

Appendix 5. Specialty Lab Schedule

		Treatment Period									Safety Follow-up
Sample	**Timepoint**	**Day 0**	**Day 2 ±1 day**	**Day 4 ±1 day**	**Day 7 ±1 day**	**Day 10±1 day**	**Week 2**	**Week 26**	**Week 52**	**Week 104, 156, 208 /EOT**	**Week 210/EOS (4 wks post last dose)**
Pamrevlumab Pk[a]	Before infusion	X					X	X	X		
	Within 1 hour after infusion	X							X		
	Time point sample (no infusion)		X	X	X	X					
HAHA[b]	Predose (when applicable)	X									X
CTGF[c]	Predose (when applicable)	X								X	
Exploratory[d]	Predose (when applicable)	X							X	X	

Abbreviations: CTGF = connective tissue growth factor; ET = early termination; HAHA = human anti-human antibody; PK = pharmacokinetic

a. Approximately 1-2 mL of blood will be collected for each measurement of pamrevlumab PK.

b. Approximately 1 mL of blood will be collected for each measurement of HAHA.

c. Blood and urine samples will be collected. Approximately 1 mL of blood and 0.5 mL of urine will be collected for each measurement of CTGF.

d. Approximately 5 mL of blood will be collected for each exploratory sample.

TITLE PAGE

CLINICAL STUDY PROTOCOL

STUDY TITLE:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
PROTOCOL NUMBER:	FGCL-3019-079
PHASE:	2
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	126630
STUDY DRUG:	Pamrevlumab (FG-3019)
INDICATION:	Duchenne Muscular Dystrophy
FIBROGEN MEDICAL MONITOR:	[redacted] FibroGen, Inc. [redacted] Telephone: [redacted] Mobile: E-mail Address: [redacted]
ORIGINAL PROTOCOL:	16 June 2015
AMENDMENT 1.0:	31 August 2015
AMENDMENT 2.0:	06 May 2016
AMENDMENT 3.0:	09 December 2016
AMENDMENT 4.0:	10 July 2017
AMENDMENT 5.0:	14 November 2017
AMENDMENT 6.0:	14 November 2018 (Site Specific – Site [redacted] and [redacted])
AMENDMENT 7.0:	27 September 2019

CONFIDENTIALITY STATEMENT

INVESTIGATOR SIGNATURE PAGE STUDY ACKNOWLEDGEMENT

Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy

FGCL-3019-079

Original: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

Amendment 3.0: 09 December 2016

Amendment 4.0: 10 July 2017

Amendment 5.0: 14 November 2017

Amendment 6.0: 14 November 2018 (Site Specific – Site [redacted] and [redacted])

Amendment 7.0: 27 September 2019

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

Please return a copy of this signature page to FibroGen's designee. Please retain the original for your study files.

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 16 June 2015

Amendment 1.0: 31 August 2015

Amendment 2.0: 06 May 2016

Amendment 3.0: 09 December 2016

Amendment 4.0: 10 July 2017

Amendment 5.0: 14 November 2017

Amendment 6.0: 14 November 2018 (Site Specific – Site [redacted] and [redacted])

Amendment 7.0: 27 September 2019

This protocol is approved by FibroGen.

[redacted]

17-Oct-19 | 14:02:31 PDT

Date

AMENDMENT 6.0: KEY CHANGES (SITE SPECIFIC – SITES [redacted] AND [redacted] ONLY)

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Amendment 6.0 changes are documented here for informational use only for sites that were not included in its distribution.

Key Change	Rationale	Sections Affected
Extended treatment duration from 156 weeks to 208 weeks, with exploratory analyses at week 208.	This allows subjects continued access to treatment, and the collection of more data.	Synopsis (Study Design, Study Procedures, Treatments), 2.5, 4.2, 7.1.2, 7.1.3, 7.1.4, 7.1.5, 7.2.6, Appendices 4 and 5.
Medical Monitor has been changed from [redacted] to [redacted]	Medical Monitor has been changed from [redacted] to [redacted]	Title Page

AMENDMENT 7.0: KEY CHANGES (ALL SITES)

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Key Change	Rationale	Sections Affected
Addition of Appendix 6: Open Label Extension (OLE) for all subjects who complete 104 weeks of treatment on the main study and complete EOT. Modifications are made in the main study to address the addition of the Appendix.	This allows subjects continued access to treatment, and the collection of more data.	Synopsis (Study Design, Study Procedures, Treatments), 2.5, 4.2, 7.1, 7.1.2, 7.1.3, 7.1.4, 7.2, 9.3.1 and Appendix 6.
Added Respiratory Muscles and Diaphragm MRI in OLE	The administrative analysis showed a reduction in muscle fibrosis which correlated well with muscle function. The same concept should apply to measure whether less fibrosis in respiratory muscles and diaphragm has any correlation with an improvement in the PFTs.	Appendix 6
Addition of 50mL vial and study drug packaging and labeling.	Provides clarity on alternate vial size and details for drug packaging and labeling.	6.1.1, 6.1.2
SAE Fax Number correction	SAE Fax Number correction	8.3.5

1. PROTOCOL SYNOPSIS

Study Title:	Trial of Pamrevlumab (FG-3019), a Monoclonal Antibody to Connective Tissue Growth Factor, in Non-Ambulatory Subjects with Duchenne Muscular Dystrophy
Protocol Number:	FGCL-3019-079, Amendment 7.0
Investigational Product:	Pamrevlumab (FG-3019) (Recombinant fully human IgG1 kappa monoclonal antibody to connective tissue growth factor)
Study Phase:	Phase 2
Target Population:	Non-ambulatory subjects with Duchenne muscular dystrophy (DMD)
Number of Subjects Planned:	Approximately 22 subjects will be enrolled; interim analysis may increase sample size to approximately 32
Study Centers Planned:	Approximately 10 centers

OBJECTIVES

Primary Objective

To estimate pamrevlumab's efficacy in non-ambulatory subjects with DMD

Secondary Objectives

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

ENDPOINTS/ASSESSMENTS

Efficacy

Primary Endpoint

- Annual change from baseline to Week 104 in percent predicted forced vital capacity (FVC) during treatment with pamrevlumab.

Secondary Endpoints

- Change from baseline to 104 weeks in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow

- Change in LVEF from baseline to Week 104
- Change from baseline to Week 104 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 104 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 104 in cardiac fibrosis score assessed by magnetic resonance imaging (MRI)
- Change from baseline to Week 104 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

Exploratory, Pharmacokinetics, Pharmacodynamics

- Pharmacokinetic (PK) profile of pamrevlumab (including C_{min}, C_{max}, AUC_{tau}, and t1/2) [In the first 12 subjects to have PK/PD samples though Day 14]
  - In the overall population
  - In subjects 12 to 16 years of age, inclusive
  - In subjects older than 16 years
  - Comparison of PK profiles across age groups
- Plasma and urine connective tissue growth factor (CTGF)
- Creatine kinase (CK)
- Circulating biomarkers
- Exploratory analyses on primary and secondary efficacy endpoints at week 156 will be conducted at the end of the study.

Safety

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

STUDY DESIGN
This study is an open-label, single arm study which will initially enroll approximately 22 subjects and includes an open label extension (OLE). Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for a minimum of 104 weeks and will transition onto the OLE within 2-3 infusions from the approval of the amendment for up to an additional 208 weeks (refer to appendix 6). An interim analysis will be conducted after at least 10 to 12 subjects have completed 52 weeks of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects. All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow).
STUDY PROCEDURES
Details regarding study procedures are provided as follows: Appendix 1: Screening Period through Week 26 Appendix 2: Week 28 through Week 58 Appendix 3 : Week 60 through Week 104 Appendix 4: Week 106 through Week 210/EOS Appendix 5: Specialty Lab Schedule Appendix 6: Open Label Extension
MAIN SELECTION CRITERIA
Inclusion Criteria Subjects must meet all of the following criteria in order to be eligible for the study: 1. At least 12 years of age 2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements 3. Non-ambulatory 4. Brooke Score for Arms and Shoulders ≤5 5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test 6. Able to perform spirometry 7. Able to undergo cardiac and extremity (upper arm) MRI 8. Percent predicted FVC between 40 and 90, inclusive 9. At least one historical FVC % predicted value within 18 months of baseline 10. Left ventricular ejection fraction ≥45% as determined by cardiac MRI at screening or within 3 months prior to Day 0 11. Subjects currently receiving heart failure cardiac medications (e.g., angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening 12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation.

13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /µL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. Gamma glutamyl transferase (GGT) ≤3x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after last dose of study drug.

Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 156 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 156 weeks
4. Severe uncontrolled heart disease including any of the following:
    a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

TREATMENTS

Pamrevlumab Dose, and Mode of Administration

Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for a minimum of 104 weeks and will transition onto the OLE within 2-3 infusions of the approval of the amendment for up to an additional 208 weeks. The dose of pamrevlumab (35 mg/kg) for the first infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken approximately every 3 months thereafter.

Concomitant Medications/Therapies:

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy. Investigational agents, and those that receive marketing authorization, or approved product for DMD (e.g. eteplirsen) during this trial are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed. Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

STATISTICAL METHODS

A total of 22 subjects is planned to achieve 80% power to test the null hypothesis of change in percent predicted FVC of -5% against the alternative hypothesis, assuming a mean change of -2% and standard deviation of 5%, based on a 2-sided one sample t-test at 0.05 significance level.

The primary efficacy endpoint will be met if the annual change in percent predicted FVC is above -5% after 104 weeks of treatment with pamrevlumab (lower bound of the 2-sided 95% confidence interval is above -5%).

An interim analysis will be conducted after at least 10 to 12 subjects have completed 1 year of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

The primary efficacy endpoint is the annual change from baseline to Week 104 in percent predicted FVC during treatment with pamrevlumab. The mean annual change in percent predicted FVC and the corresponding 2-sided 95% confidence interval will be presented.

Final analysis of the primary and secondary endpoints will be described in the statistical analysis plan. Details of the interim analysis will be described in an interim analysis plan.

Pamrevlumab concentrations and derived PK parameters will be tabulated and summarized using descriptive statistics. Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters. Attainment of steady-state will be investigated.

Safety analyses will include summary of adverse events (including treatment emergent AEs, treatment emergent serious AEs, deaths, and infusion-associated AEs), prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs), and physical exams.

TABLE OF CONTENTS

2. INTRODUCTION

2.1. Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G1 (IgG) kappa monoclonal antibody to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role. These diseases include liver fibrosis due to hepatitis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne muscular dystrophy (DMD). Pamrevlumab (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. Pamrevlumab contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2. Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is usually inherited in an X-linked recessive fashion, but it can occur as a result of spontaneous mutation in boys from families without a known history of the condition. On the basis of some 40 studies including several million male births, incidence at birth of Duchenne muscular dystrophy is around 1:3300, and its prevalence in the population (in terms of the total male population) is around 1:16500 (Emery, 1991).

DMD is a result of mutations (mainly deletions) in the dystrophin gene (DMD; locus Xp21.2). Mutations lead to an absence of or defect in the protein dystrophin, which results in progressive muscle degeneration with loss of independent ambulation by the age of 13 years (Bushby, 2010).

In skeletal muscles of DMD patients constant myofiber breakdown results in persistent activation of myofibroblasts and altered production of extracellular matrix (ECM) resulting in extensive fibrosis. Muscle fibrosis is the only myo-pathologic parameter that significantly correlated with poor motor outcome as assessed by quadriceps muscle strength, manual muscle testing of upper and lower limbs, and age at ambulation loss (Desguerre, 2009).

Patients with DMD are generally wheelchair bound before they develop significant respiratory muscle weakness. Respiratory complications are the primary cause of morbidity and mortality in DMD as progressive respiratory muscle weakness leads to hypoventilation and/or recurrent atelectasis and pneumonia, secondary to decreased cough effectiveness (McKim, 2012).

After age 10 to 14, patients gradually begin to lose respiratory muscle function based on pulmonary function tests (PFTs) such as forced vital capacity (FVC). The median loss in FVC (% predicted) is estimated to be 8.0% per year (Phillips, 2001, Tangsrud, 2001).

Because of improvements in respiratory care, cardiac dysfunction is now a leading cause of morbidity and mortality in DMD patients (Schram, 2013). Progressive myocardial fibrosis, as detected by late gadolinium enhancement (LGE), is strongly correlated with the left ventricular ejection fraction (LVEF) decline in Duchenne muscular dystrophy patients. Longer steroid treatment duration is associated with a lower age-related increase in myocardial fibrosis burden (Tandon, 2015).

2.2.1. Relevance of Connective Tissue Growth Factor (CTGF) in DMD

Connective tissue growth factor (CTGF) is a nonstructural regulatory protein present in the extracellular matrix that has an important role in fibrosis. Skeletal muscle from DMD patients, dystrophic dogs, and mdx mice all show elevated levels of CTGF (Sun, 2008).

CTGF can reproduce or amplify the effects of TGFβ on fibrosis by inducing collagen type 1, α5 integrin, and fibronectin much more potently than TGFβ in fibroblasts (Kharraz, 2014).

Comparison of mdx mice with normal or genetically depleted levels of CTGF revealed that exercised mice with reduced CTGF developed less fibrosis and exhibited better muscle strength than mice with normal levels of CTGF (Morales, 2013). In culture, both myoblasts and myotubes were shown to express and secrete CTGF to the medium, and respond to the growth factor by increasing the extracellular matrix constituents, partially inhibiting myoblasts differentiation and inducing myoblasts dedifferentiation (Vial, 2008).

In DMD, the role of CTGF might extend well beyond replacement fibrosis secondary to loss of muscle fibers, since its overexpression in skeletal muscle could by itself induce a dystrophic phenotype (Morales, 2013).

A major feature of the hearts of DMD patients is cardiac fibrosis. Cardiac fibrosis is associated with increased CTGF expression in the mdx mouse heart. CTGF may be a key mediator of early and persistent fibrosis in dystrophic cardiomyopathy (Au, 2011).

CTGF is critically involved in several chronic fibro-degenerative diseases. Pamrevlumab treatment has been shown to positively the affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.

2.3. Summary of Relevant Findings from Nonclinical and Clinical Trials

Please refer to the most recent version of pamrevlumab Investigator's Brochure.

2.3.1. Nonclinical Studies

In DMD, the genetic loss of the cytoskeletal protein dystrophin results in muscle damage that, leads to progressive replacement of muscle with fibrotic and fat tissue. This progressive muscle damage can be recapitulated in the DMD mouse model (mdx), and accelerated by muscle usage (Pessina, 2014).

As was observed with genetic depletion of CTGF, pharmacologic inhibition of active CTGF in mdx mice by treatment with pamrevlumab resulted in reduced fibrosis and skeletal muscle damage, as well as improved preservation of skeletal muscle strength in isolated muscles. The pamrevlumab treated mdx mice were also subjected to a test of exercise endurance, in which they showed better performance than mdx mice injected with control IgG (Morales, 2013).

Pamrevlumab treatment of mdx mice was associated with decreased skeletal muscle damage and fibrosis, decreased collagen III and fibronectin expression, decreased plasma creatine kinase (CK) (Morales, 2013), and increased isometric force of skeletal muscle (Morales, 2011).

2.3.2. Pharmacokinetics

Key findings are summarized below from Phase 1 and 2 studies investigating the pharmacokinetics (PK) of pamrevlumab in subjects with diabetic kidney disease, idiopathic pulmonary fibrosis, liver fibrosis and pancreatic cancer:

- Pamrevlumab was administered over the dose range of 3 to 45 mg/kg every 2 weeks, every 3 weeks, and 17.5 to 22.5 mg/kg weekly.
- Pamrevlumab exposure (e.g., mean/median Cmax and Cmin, area under the curve [AUC]) generally increased with increasing dose.
- For single dose studies, for doses > 10 mg/kg the t1/2 did not appear to increase with increasing pamrevlumab doses, based on available data with estimated mean t1/2 values of approximately 1 week.
- For multiple dose studies, the mean t1/2 following multiple doses (3 to 10 mg/kg) also increased from 102 to 135 hours.
  - The estimated t1/2 values for doses > 10 mg/kg did not appear to increase markedly with dose, based on available data (limited time points).

2.3.3. Safety

Key findings are summarized below from the Phase 1 and 2 studies involving more than 400 adults with diabetic kidney disease, idiopathic pulmonary fibrosis, and liver fibrosis due to hepatitis B or pancreatic cancer:

- Overall, pamrevlumab was well tolerated across the range of doses noted above, and there were no dose-limiting toxicities.
- Treatment-emergent adverse events (TEAEs) were generally mild or moderate in severity and transient in duration.
- Infusion-related reactions have been mild-to-moderate and are considered an identified risk of pamrevlumab administration.
- TEAEs were considered typical of the subjects' underlying medical condition(s) and, in the placebo-controlled studies, were equally distributed between placebo and pamrevlumab treatment groups.
- No apparent pattern to TEAEs that occurred within 24 hours after infusions was observed.
- No apparent pattern for treatment-emergent serious adverse events (TESAEs) was observed during clinical testing.

2.3.4. Efficacy

Key efficacy findings are summarized below from the Phase 1 and 2 studies of CTGF inhibition by pamrevlumab in indications other than DMD.

2.3.4.1. Pancreatic Cancer

Biweekly doses of up to and including 45 mg/kg and weekly doses of 17.5 and

22.5 mg/kg were administered to subjects with previously untreated locally advanced or metastatic pancreatic adenocarcinoma. Increased exposure to pamrevlumab was associated with increased survival. There appears to be a relationship between survival and trough blood levels of pamrevlumab (Cmin). Notably Cmin >150 mcg/mL after the first dose of pamrevlumab (Day 15) was associated with significantly increased progression free survival and overall survival.

A maximal effect in survival benefit was achieved at dose levels of 25 to 45 mg/kg/2 weeks.

2.3.4.2. Idiopathic Pulmonary Fibrosis (IPF)

In subjects with IPF who completed 45 weeks of dosing with 15 or 30 mg/kg pamrevlumab, approximately 40% of subjects had stable or improved lung fibrosis by quantitative high resolution CT imaging compared to baseline values with approximately 30% having improved pulmonary fibrosis.

Overall, subjects with stable or improved lung fibrosis also had stable or improved FVC (% predicted).

2.4. Risks and Benefits

Pamrevlumab has been generally well tolerated with most adverse events being typical of those expected for subjects with the underlying disease conditions.

Infusion-related reactions have been observed in some subjects treated with pamrevlumab. Across studies in other indications, infusion-related reactions have been mild-to-moderate did not result in discontinuation of treatment with pamrevlumab, and did not result in the use of prophylaxis for subsequent infusions.

The favorable experience with pamrevlumab to date does not exclude the possibility of more severe infusion reactions occurring in future subjects.

This is the first clinical study of pamrevlumab in DMD. There are currently no confirmed benefits to subjects with DMD treated with pamrevlumab. However, a potential benefit of treatment with pamrevlumab is indicated in preclinical models of DMD and previous clinical studies of pamrevlumab in other indications where CTGF is also associated with disease progression.

Dose regimens equal to or exceeding 35 mg/kg have been implemented in other indications in adult subjects. The objective of these studies was to inhibit bioactive CTGF, which is associated with disease progression in a number of indications. Please refer to the Investigator's Brochure for a comprehensive summary of efficacy, safety, and exposure data.

The current study will explore the clinical relevance of CTGF inhibition, as indicated in preclinical models, in DMD patients.

2.5. Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Periods

Pamrevlumab is administered as an IV infusion at a dose of 35 mg/kg every two weeks (Main study Day 0 to a minimum of Week 104, and OLE Day 0 up to Week 208/EOT). The dose, frequency and route of administration correspond with dose regimens that were well tolerated and possibly associated with efficacy in clinical studies in adults with IPF and pancreatic cancer. In both of these indications pamrevlumab was administered at doses that included the targeted dose regimen for the current study (35 mg/kg bodyweight) and greater (45 mg/kg bodyweight). These doses were not associated with dose limiting toxicity.

The overall objective of all of these studies, including the current study, is to provide a dose associated with clinically relevant CTGF blockade to impede progression of serious disease states. Body weight-related dosing and utilization of a dose no greater than the maximal dose used in adults are expected to ensure that systemic exposure in the targeted pediatric population will not exceed the systemic exposure achieved in adults.

PK assessments will be done during the course of the study and facilitate ongoing monitoring of exposure to pamrevlumab during the course of the study.

The planned treatment duration is no longer than total treatment periods achieved in previous studies with pamrevlumab.

The duration of treatment of the current study is also similar to the duration of other studies in DMD and is expected to provide sufficient basis to evaluate potential benefit in the targeted pediatric population with DMD.

2.6. Good Clinical Practice and Regulatory Requirements

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents. Detailed information regarding study conduct is found in Sections 10, 11, 12, and 13.

2.7. Population to be Studied

Non-ambulatory adolescents and adults with DMD will be enrolled in this trial. A detailed inclusion/exclusion list is provided in Section 5.

3. OBJECTIVES

3.1. Primary Objective

The primary objective of this trial is to estimate pamrevlumab's efficacy in non- ambulatory subjects with DMD.

3.2. Secondary Objectives

The following are the secondary objectives of this trial:

1. To evaluate safety and tolerability of pamrevlumab administered intravenously every 2 weeks
2. To assess pharmacokinetics of pamrevlumab in the targeted pediatric population
3. To evaluate pharmacodynamic markers of pamrevlumab's effects in DMD

4. STUDY DESIGN

4.1. Endpoints and Assessments

4.1.1. Primary Endpoint

The primary endpoint is the annual change from baseline to Week 104 in percent predicted forced vital capacity (FVC) during treatment with pamrevlumab.

4.1.2. Secondary Endpoints

The following are the secondary endpoints:

- Change from baseline to Week 104 in forced expiratory volume (FEV1), maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), peak expiratory flow (PEF), peak cough flow
- Change in LVEF from baseline to Week 104
- Change from baseline to Week 104 in Performance of Upper Limb (PUL) Score
- Change from baseline to Week 104 in grip strength, pinch strength, and Brooke scale for upper extremity
- Change from baseline to Week 104 in cardiac fibrosis score assessed by MRI
- Change from baseline to Week 104 in upper arm (bicep) muscle fat and fibrosis assessed by MRI

4.1.3. Exploratory, Pharmacokinetic and Pharmacodynamic Outcome Measures

Exploratory outcome measures for this trial are:

- Pharmacokinetic (PK) profile of pamrevlumab (including Cmin, Cmax, AUCtau, and t1/2) [In the first 12 subjects to have PK/PD samples though Day 14]
  - In the overall population
  - In subjects 12 to 16 years of age, inclusive
  - In subjects older than 16 years
  - Comparison of PK profiles across age groups
- Plasma and urine CTGF
- Creatine kinase (CK)
- Circulating biomarkers
- Exploratory analyses on primary and secondary efficacy endpoints at week 156 will be conducted at the end of the study.

4.1.4. Safety Assessments

Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests and discontinuation of treatment for treatment-related AEs serve as the safety assessments for this trial.

4.2. Trial Overview

This study will be an open-label, single arm study that will initially enroll approximately 22 subjects and includes an open label extension (OLE). Each subject will receive pamrevlumab (35 mg/kg, every 2 weeks) for a minimum of 104 weeks and will transition onto the OLE within 2-3 infusions from the approval of the amendment An interim analysis will be conducted after at least 10 to 12 subjects have completed 1 year of treatment. As a result, sample size may be readjusted to a total of approximately 32 subjects.

All subjects will be closely monitored for safety (including trends of pulmonary function tests: FVC, mean inspiratory flow, and peak expiratory flow) on a continuous basis.

Upon completion of treatment or premature discontinuation from the trial, subjects will be asked to return to the investigative site to complete final safety and efficacy assessments.

4.3. Study Treatment

4.3.1. Dose and Schedule

Each subject will receive pamrevlumab (35 mg/kg) intravenously every 2 weeks (q2w). See Section 6 for detailed information on study drug formulation, storage, and administration.

4.3.2. Rationale for Dose and Schedule

The pamrevlumab dose is based on results of a study in adult subjects with pancreatic cancer. In that study (Section 2.3.4.1), minimum pamrevlumab blood levels (Cmin)

≥150 mcg/mL were associated with increased median survival and 1 year survival compared to subjects with Cmin <150 mcg/mL. Given the apparent threshold effect for increased benefit when minimal pamrevlumab exposure is ≥150 mcg/mL and based on PK analysis using these data, the planned dose of 35 mg/kg administered every 2 weeks is projected to achieve this minimum exposure in the targeted DMD study population.

4.4. Concomitant Medications, Procedures and Nondrug Therapies

Subjects will receive full supportive care as required by their clinical condition. Management of corticosteroid dose is up to the discretion of the physician. All subjects should be monitored for osteoporosis in accordance with the respective institutional standard of care for DMD patients receiving glucocorticoid therapy.

Investigational agents, and those that receive marketing authorization during this trial, or approved product for DMD (e.g. eteplirsen) are prohibited. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

Concomitant medications (any prescription and/or over-the-counter [OTC] preparation) and procedures or nondrug therapies (e.g., physical therapy or acupuncture) used by a subject while

participating in this clinical trial must be recorded from the Screening Visit through the End-of-Study Visit.

Questions regarding potential impact of concomitant medications on evaluability of subjects should be addressed to the attention of the FibroGen Medical Monitor.

4.4.1. Contraception

Subjects with female partners of childbearing potential are required to use two forms of contraception during the conduct of the study and for 3 months after the last dose of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy of a partner must be reported (Section 8.3.6).

4.5. Safety Plan

An ongoing safety review is facilitated by the unblinded nature of the study. FibroGen will review safety data and will communicate the results of these reviews to investigators by email or teleconference on a regular basis. In addition, FibroGen will review safety experience with investigators during teleconferences that will be held at least quarterly and include the conclusions of the Data Monitoring Committee's (DMC) latest data review.

FibroGen will notify investigators immediately if a new safety risk is identified.

4.6. Data Monitoring Committee

A DMC will be utilized and will be composed of external experts. Composition and responsibilities of the DMC are defined in a separate DMC charter.

DMC responsibilities include review of safety data, and may include available pharmacokinetic data, and pulmonary function tests.

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Inclusion Criteria

Subjects must meet all of the following criteria in order to be eligible for the study:

1. At least 12 years of age
2. Written consent/assent by patient and/or legal guardian as per regional and/or IRB requirements
3. Non-ambulatory
4. Brooke Score for Arms and Shoulders ≤5
5. Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
6. Able to perform spirometry
7. Able to undergo cardiac and extremity (upper arm) MRI
8. Percent predicted FVC between 40 and 90, inclusive
9. At least one historical FVC % predicted value within 18 months of baseline
10. Left ventricular ejection fraction ≥45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
11. Subjects currently receiving heart failure cardiac medications (e.g. angiotensin converting enzyme inhibitors, angiotensin-receptor blockers, and beta-blockers) must achieve a stable regimen for at least 3 months prior to screening
12. On a stable dose of corticosteroids for a minimum of 6 months prior to screening with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening and no foreseen change in corticosteroid use during the course of study participation
13. Received pneumococcal vaccine and is receiving annual influenza vaccinations
14. Adequate renal function: cystatin C ≤1.4 mg/L
15. Adequate hematological function:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /µL
16. Adequate hepatic function:
    a. No history or evidence of liver disease
    b. gamma glutamyl transferase (GGT) ≤3 x upper limit of normal (ULN)
    c. Total bilirubin ≤1.5xULN
17. If sexually active, will use medically accepted contraceptives during participation in the study and for 3 months after the last dose of study drug

5.2. Exclusion Criteria

Subjects must not meet any of the following criteria in order to be eligible:

1. Requires ≥16 hours continuous ventilation
2. Prior or ongoing medical condition that in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of 156 weeks of treatment and follow-up would be completed, or could impair the assessment of study results
3. Anticipated spine surgery within 156 weeks
4. Severe uncontrolled heart disease including any of the following:
   a. Need for intravenous diuretics or inotropic support within 3 months prior to screening
   b. Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
5. Arrhythmia requiring anti-arrhythmic therapy
6. Hospitalization due to respiratory failure in the last 6 weeks
7. Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
8. Known or suspected active hepatitis B or C or history of HIV
9. BMI ≥40 kg/m^2 or weight >117 kg
10. Exposure to another investigational drug or another approved product for DMD (e.g. eteplirsen) within 28 days prior to start of study treatment (or 5 half-lives of the product whichever is longer) prior to first screening visit with the exception of deflazacort. Use of deflazacort if regarded by the principal investigator as standard of care is allowed.

5.3. Subject Withdrawal

Subjects may withdraw from the study at any time.

The investigator may remove a subject from study treatment for the following reasons:

- Adverse events, which in the opinion of the Principal Investigator and/or FibroGen preclude further study drug dosing
- Nonadherence to protocol-defined procedures, in particular missing of 3 or more sequential study drug infusions
- Not available for safety assessments

Subjects who discontinue the study early should be strongly encouraged to complete the evaluations described in Section 7.1.3.

5.4. Replacement of Subjects

Subjects may be replaced in this study if a subject’s participation is not terminated due to safety or tolerability issues and is replaced prior to completion of targeted recruitment into the study. Replacement decisions will be made between the sponsor and investigator on a case-by-case basis.

5.5. Study Termination

This trial can be terminated by the sponsor at any time for any reason.

6. STUDY DRUG/TREATMENT SUPPLY

6.1. FibroGen Investigational Product

Pamrevlumab is a fully human IgG1 kappa monoclonal antibody that binds to CTGF.

6.1.1. Formulation

Pamrevlumab is supplied in single-use glass vials containing 10 mL or 50 mL of a sterile, preservative-free solution (100 mg pamrevlumab/vial or 500 mg pamrevlumab/vial respectively). The solution is composed of 10 mg/mL pamrevlumab, 1.60 mg/mL l-histidine, 3.08 mg/mL l-histidine HCl, 8.01 mg/mL sodium chloride and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0. If different vial sizes or new formulations are introduced during the course of the study, updates to formulation, storage, etc. will be provided through an amendment to the Pharmacy Manual and investigative site staff training.

6.1.2. Study Drug Packaging and Labeling

Labels will be prepared and will comply with Good Manufacturing Practice and USA regulatory guidelines.

6.1.3. Storage

Vials of pamrevlumab must be stored refrigerated (2°C to 8°C), in a temperature- controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation.

6.1.4. Preparation of Dose for Administration

The dose of pamrevlumab (35 mg/kg) for the first infusion should be based on body weight obtained during screening. Dose will be adjusted based on body weight taken every 3 months thereafter. Pamrevlumab may be administered undiluted or, for convenience of infusion, may be diluted with 0.9% Sodium Chloride Injection according to the Dose Preparation Instructions in the Study Reference Investigational Product (IP) Manual.

Pamrevlumab will be administered as soon as possible after release from the site’s pharmacy and within 24 hours of preparation. Pamrevlumab will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

6.1.5. Administration

Study Drug	Dose	Route	Infusion Rate	Schedule
Pamrevlumab	35 mg/kg	IV	Not to exceed 150 cc/hour	Every 2 weeks
DO NOT ADMINISTER PAMREVLUMAB AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.				

Subjects who weigh more than 117 kg will receive the maximum allowed dose of 4.1 g. For this study, the overall rate of infusion for the prepared study drug should not exceed 150 cc/hour. Adjustments may be made to further slow the rate of infusion (infusing less than 150 cc/hour) in accordance with the investigator's clinical judgement. Subjects should be carefully monitored for reaction during the first infusion with a physician available as needed. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation. The IV access should remain in place and be maintained per site procedures until the end of this post treatment observation period. If a subject has an infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences an infusion reaction and continues pamrevlumab dosing, a physician must be immediately available during subsequent infusions and observation periods until the subject does not have any infusion reaction for three sequential infusions.

Premedication, such as antihistamines, corticosteroids or nonsteroidal anti-inflammatory drugs (NSAIDs) are not normally administered before infusions of pamrevlumab.

Premedication may be used for subjects who experience infusion reactions at the discretion of the investigator after discussion with the Medical Monitor.

Pamrevlumab will be administered in a hospital or ambulatory setting with adequate facilities for managing medical emergencies for at least three infusions to confirm the subject does not have an infusion reaction. The study site must have trained staff and medications for the treatment of acute reactions, including anaphylaxis, immediately available. There is no specific treatment for a pamrevlumab overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

FibroGen may consider the use of properly trained home health care staff to administer the pamrevlumab infusions in the future and corresponding study assessments during the conduct of the study, consistent with institutional regulations and policies.

7. ASSESSMENT OF EFFICACY AND PHARMACOKINETICS

7.1. Study Procedures by Visit

All study procedures and assessments for the main study will be performed in accordance with the Schedule of Assessments presented in Section 16 and in Appendix 6 for the OLE.

For all potential subjects, screening procedures required to determine subject eligibility will be performed within 28 days prior to Day 0 (first infusion of pamrevlumab).

Potential subjects may be re-screened if initial screening procedures lie outside the 28-day screening period prior to planned study entry.

Subject's eligibility for this study will be reviewed and approved by Sponsor's medical monitor prior to subject enrollment.

The following assessments are relevant to the assessment of efficacy: pulmonary function tests (FVC, mean inspiratory flow (MIF), peak expiratory flow), Brooke Upper Extremity Rating Scale, Performance of the Upper Limb, pinch strength, grip strength, cardiac MRI, and muscle MRI. Refer to the Study Reference Manual for details.

Approved windows for performing study assessments are defined in the following sections.

7.1.1. Screening Period (no earlier than Day -28)

Assessments to be conducted during the screening period are presented in Appendix 1.

Screening assessments may be completed over several visits during the screening period. It is recommended that the less invasive screening assessments be performed first upon completion of the signed Informed Consent and/or Assent Form [ICF] (demographics, medical history, blood draws, electrocardiogram [ECG], vital signs (includes body weight and height), physical exam, pulmonary function tests (PFTs), and then followed by the more rigorous screening assessments (i.e., muscle function tests, cardiac MRI).

A cardiac MRI performed within 3 months prior to Day 0 (start of dosing) is acceptable to confirm eligibility based on the LVEF study entry criterion and as baseline cardiac MRI. If an historic MRI is not available, a cardiac MRI must be performed during the Screening Period.

An upper arm muscle MRI is not required to determine subject eligibility at screening, but may be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Muscle and pulmonary function tests (PFTs) will be performed during the screening period. Muscle function and PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.

If the subject cannot perform adequately due to illness (e.g. sinusitis, etc.) then the PFTs should be delayed until the subject can reliably perform the assessment within the 28-day screening window.

In addition, an exploratory blood sample will be drawn for analysis of circulating biomarkers of fibrosis and specific muscle miRNAs (dystromirs) prior to first pamrevlumab infusion.

7.1.2. Dosing Period

The dosing period begins on the first day of dosing with study treatment (Day 0) and continues for a minimum of 104 weeks. Subjects will transition onto the OLE within 2-3 infusions from the approval of the amendment. Subjects will receive study drug every 2 weeks.

The visit window for all dosing visits is ±2 days. Visits should be scheduled based on the previous visit, not the baseline visit.

Assessments and procedures to be performed during the dosing period are presented in Section 16.

Muscle or pulmonary function tests that cannot be performed or produce inadequate results according to test procedures during a specified visit should be performed by the next scheduled dosing visit.

Both cardiac and muscle MRIs may be performed within ±2 weeks of the specified visit.

Blood samples will be drawn for pharmacokinetic analysis according to the schedule in Appendix 5. Blood draws to be collected on non-dosing days may be collected within ±1 day as outlined in Appendix 5.

7.1.3. End of Treatment

Assessments and procedures to be conducted after the last dose of study drug on the main study are presented in Appendix 4 .

All subjects who complete 104 weeks of treatment will be offered continued participation via the OLE. If the subject consents to ongoing treatment, the EOT MRIs must be performed within 7 days of EOT.

7.1.4. Early Withdrawal from Treatment and Safety Follow-up Period

Subjects who prematurely discontinue the main study should be strongly encouraged to complete the final efficacy evaluations scheduled for Week 208/EOT as applicable, and the safety follow-up evaluations scheduled for the Week 210/EOS visit (4 weeks following the last dose).

Subjects who withdraw prior to week 104 will not be eligible to participate in the OLE.

7.1.5. Safety Follow-Up Period

For all subjects, the final safety assessments should be completed at the Week 210/EOS visit, 4 weeks (±7 days) after the last dose of pamrevlumab.

7.1.6. Missed Visits

Every attempt must be made to complete all study visits as outlined in the Schedules of Assessments. Missed infusions will not be replaced. If a subject misses a scheduled efficacy assessment, the assessment should be performed as soon after the missed visit as feasible and within the windows specified above.

7.1.7. Unscheduled Visits

Unscheduled Visit assessments may be required at the discretion of the investigator.

7.2. Assessments

Please refer to the Schedules of Assessments for both the main study and OLE (Section 16) for the scope and timing of assessments. Please refer to the Laboratory Manual for details regarding laboratory sample collection and processing; and the Study Reference Manual for details regarding the conduct of functional tests and MRIs.

7.2.1. Pulmonary Function Tests

The following pulmonary function tests (PFTs) will be performed to assess changes in lung function: forced vital capacity (FVC), maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP) and peak expiratory flow rate (PEF; PEFR), forced expiratory volume in 1 second (FEV1), and peak cough flow (Mayer, 2015, Miller, 2005).

7.2.2. Muscle Strength and Functional Measurements

The following assessments will be performed to assess changes in upper extremity strength and function: Brooke Upper Extremity Rating Scale (Brooke Scale), Performance of the Upper Limb (PUL), Grip Test, and Pinch Strength Test.

7.2.3. Cardiac MRI

Cardiac MRIs will be performed as per Section 16 to assess changes in left ventricular ejection fraction (LVEF) and presence of late gadolinium enhancement (LGE), a marker for myocardial fibrosis.

7.2.4. Muscle MRI

An upper arm muscle MRI at screening, will be conducted within the screening period (4 weeks prior to Day 0) or anytime up to Week 4 dosing visit (4 weeks after Day 0). The results of this assessment are acceptable as baseline assessment.

Upper arm (bicep) muscle MRIs will be performed as per Section 16.

7.2.5. Quality of Life Questionnaire

Pediatrics Outcomes Data Collection Instrument (PODCI) Quality Outcome Questionnaire will be performed to assess if treatment with pamrevlumab improves quality of life.

7.2.6. Vital Signs and Physical Examinations

A physical examination will be performed at screening and baseline (Day 0), approximately every 12 weeks and at Week 208/EOT. Complete physical exams will be performed at screening, Week 48, Week 104, Week 156, and Week 208/ EOT. Other examinations may be disease-specific or problem-oriented examinations.

Vital signs (pulse, respiration, sitting blood pressure, and temperature) will be collected at screening and at all visits. During infusion visits, vital signs will be collected prior to start of

each infusion, within 15 minutes of the end of each infusion, and within 15 minutes of the completion of the post-infusion observation period.

7.2.7. Laboratory Assessments

All laboratory tests of blood and/or urine specimens will be performed at a central laboratory or FibroGen, as appropriate. A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local clinical laboratories will be used to assess and facilitate the management of adverse events and to provide usual standard of care (including blood draws required prior to MRIs). Local clinical laboratory data will not be collected in the study database except for hematocrit values provided with imaging data.

7.2.7.1. Safety Assessments

Blood samples will be 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.

Safety labs will be drawn at the site's local lab prior to MRIs to ensure there is no contraindication to MRI. Hematocrit should be included in the local lab draw as these results are required to assess fibrosis and will be provided to the central imaging vendor along with the MRI scans. Details are included in the Imaging Manual.

7.2.7.2. Pharmacokinetics

Plasma concentrations of pamrevlumab will be determined on Day 0 pre-dose and within 1 hour post infusion, then on Days 2, 4, 7, 10, and 14. The Day 14 sample should be on the same day of, but prior to the start of the next infusion of study drug.

Day 2, 4, 7, and 10 PK assessments represent target days following the first dose; however, actual sample collection time of up to ±1 day of the target time is acceptable as

long as the actual time of dosing and actual time of each sample collection are recorded accurately.

At Weeks 26 and 52, trough pamrevlumab levels (Cmin) will be determined prior to study drug infusion.

PK samples will also be drawn within 60 minutes of infusion completion at Week 52.

7.2.7.3. Plasma and Urine CTGF

Plasma and urine samples will be analyzed for CTGF concentrations from samples taken as described in Appendix 5.

7.2.7.4. HAHA

Blood samples will be drawn for analysis of human anti-human antibody (HAHA) according to the schedule in Appendix 5.

7.2.7.5. Biomarkers

Blood samples will be drawn for analysis of biomarkers according to the schedule in Appendix 5. The exact biomarkers will be based on current scientific knowledge regarding CTGF, pamrevlumab and DMD at the time the tests are performed. No genetic testing will be performed.

8. ASSESSMENT OF SAFETY

8.1. Background

Adverse event reports from investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Section 16. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all SAEs, regardless of whether the investigator believes they are related to the Study Drug.

8.2. Definitions

8.2.1. Definition of an Adverse Event (AE)

For the purpose of this study, an AE is any untoward medical occurrence that occurred in the protocol-specified AE reporting period, and which does not necessarily have a causal relationship with the study drug. An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the

protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 8.3.1).

8.2.2. Definition of a Serious Adverse Event (SAE)

A serious adverse event is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the investigator or sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be an SAE.

Scheduled hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

8.2.3. Definition of an Infusion Reaction

Infusion reactions are immunologic reactions to an infused protein, and are different from events resulting from the process of infusing the protein (e.g., infusion site bruise) and are different from adverse events due to the infused protein's intended or unintended pharmacologic effects.

8.2.4. Acute Infusion Reaction

An acute infusion reaction is one that meets both of the following criteria:

1. Occurs during or within 1 hour after infusion; and
2. Clinical manifestations consistent with:
    a. IgE-mediated and non-IgE mediated hypersensitivity reactions, including but not limited to urticaria, skin rashes, angioedema, laryngeal edema, bronchospasm, gastrointestinal symptoms and hypotension; or
    b. Cytokine release syndrome, including but not limited to fever, respiratory symptoms without the presence of wheezing, tremors, chills, flushing, pruritus, changes in blood pressure, dyspnea, chest discomfort, back pain, nausea, vomiting, diarrhea, and skin rashes.

8.2.4.1. Delayed Infusion Reaction

A delayed infusion reaction is one that meets both of the following criteria:

1. Occurs ≥1 hour after the infusion
2. Clinical manifestations as described above.

8.2.4.2. Reporting Possible and Confirmed Infusion Reactions

Both acute and delayed infusion reactions will be captured as AEs and also be reported to the medical monitor within 24 hours. See Study Reference Manual for additional details.

8.2.5. Special Situations

Certain safety events, called 'Special Situations' that occur in association with the study drug(s) include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving the medicinal product (with or without subject/patient exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

Special Situations will be reported to the sponsor or designated vendor within 24 hours on a Medication Error report form. See Study Reference Manual for details.

8.3. Procedures for Eliciting, Recording, and Reporting Adverse Events

8.3.1. Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 4 weeks after the last dose of study drug, except for pregnancy reporting (Section 8.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded. The investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 8.3.5).

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

8.3.2. Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever is possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff.

New indications for medications started during the AE reporting period (i.e., after informed consent is obtained until 4 weeks after the last dose of study drug) will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the Investigator to meet the specified criteria.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)
- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

8.3.3. Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) v 4.0 guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild:** Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; ; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death:** Fatal AE.

8.3.4. Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- Related:
  - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re- occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.

- Not Related:
  - The event represents a pre-existing underlying disease that has not worsened on study
  - The event has the same characteristics of a known side-effect associated with a co-medication
  - The event is an anticipated medical condition of anticipated severity for the study population
  - The most plausible explanation for the event is a factor that is independent of exposure to study drug

8.3.5. Reporting Serious Adverse Events on the SAE Report Form

An SAE must be reported to the Sponsor and/or its designated safety management vendor within 24 hours of becoming aware of the SAE.

To report an SAE, the investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

The contact information for SAE reporting is as follows:

U.S. Toll-Free Fax Number: [redacted]-Email: [redacted]

8.3.5.1. Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the investigator that it intends to submit to global regulatory authorities.

8.3.5.2. Deaths

The investigator will report the fatal or life-threatening event immediately to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 8.3.5.

If the death occurred within the AE collection and reporting period (signed ICF to

4 weeks after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form in the same manner as described above in Section 8.3.5. Additionally, the site must complete the appropriate CRF page.

8.3.6. Pregnancies: Reporting and Follow-up of Subjects

The outcome of all pregnancies should be followed up and documented as described. Consent must be obtained from male subject's partner to collect information related to the pregnancy and outcome (and will be handled on a case-by-case basis with IRB/IEC approval). A Pregnancy Report Form must be completed and submitted to Sponsor or designated safety management vendor within 24 hours of the investigator becoming aware of the pregnancy. The investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the investigator becoming aware of the outcome.

8.3.7. Abnormal Laboratory Findings

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. The investigator must review and assess all laboratory results throughout the study in a timely manner, and determine whether any abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs. Laboratory abnormalities should be considered clinically significant when they occur after taking study medication, reflect a meaningful change from the screening value(s), and require active management (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

9. STATISTICAL CONSIDERATIONS

9.1. Sample Size Determination

This study tests the hypothesis of whether pamrevlumab can attenuate the annual decline from baseline to Week 104 in FVC in non-ambulatory DMD patients. A total of 22 subjects is planned to achieve 80% power to test the null hypothesis of change in percent predicted FVC of -5% against the alternative hypothesis, assuming a mean change of -2% and standard deviation of 5% based on 2-sided one sample t-test at 0.05 significance level. The hypotheses are:

H0: change in percent predicted FVC less than or equal to -5%

Ha: change in percent predicted FVC greater than -5%.

The primary efficacy endpoint will be met if the annual change in percent predicted FVC is greater than -5% at the end of the study (lower bound of 2-sided 95% confidence interval is greater than -5%).

9.2. Analysis Populations

9.2.1. Safety Population

The Safety Population will consist of all subjects who have received any dose of pamrevlumab. This population is also defined as the intent-to-treat (ITT) population.

9.2.2. Full Analysis Set Population

The Full Analysis Set Population (FAS) will consist of all subjects in the Safety Population who have at least one evaluable post-baseline FVC assessment.

9.3. Statistical Analysis

9.3.1. General Considerations

Descriptive summaries will be provided for all study parameters including baseline characteristics, safety, efficacy, pharmacokinetic and pharmacodynamic parameters. Continuous variables will be reported using number of subjects, mean, standard deviation or standard error, median, minimum, and maximum. In general, standard deviation is provided to describe the distribution of a parameter, such as baseline, safety, and PK/PD parameters; standard error is provided for statistical analyses of efficacy endpoints. Geometric mean will be included for PK/PD variables. Categorical variables will be reported by the frequency and percentage of subjects within each outcome category. Two-sided 95% confidence intervals will be presented for key efficacy parameters and two-sided 90% confidence intervals for PK/PD parameters. All statistical tests will be performed at α=0.05 level of significance, using two-sided tests, unless otherwise stated. Assessments as well as derived parameters will be presented in data listings for all subjects in the ITT/Safety Population.

Statistical consideration for the OLE are included in Section 16, Appendix 6. Detailed description of the analyses and summaries of efficacy and safety will be presented in the SAP.

9.3.2. Subject Enrollment and Disposition

The number of subjects in each study population as well as subject completion status and reasons for early discontinuation will be summarized.

9.3.3. 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, and quality of life parameters.

9.4. Efficacy Analyses

Efficacy analyses will be based on the FAS population. Rules of handling missing data will be described in the Statistical Analysis Plan (SAP). Analyses based on observed data will be performed for sensitivity evaluation.

9.4.1. Primary Endpoint

The primary endpoint is the annual change from baseline to Week 104 in percent predicted FVC during treatment with pamrevlumab. The mean annual change in percent predicted FVC and the corresponding 2-sided 95% confidence interval will be presented. The primary efficacy endpoint will be met if the lower bound of 2-sided 95% confidence interval is greater than -5%.

9.4.2. Analyses of Other PFT Parameters

Changes from baseline to Week 104 in other PFT parameters will be estimated similarly; details of missing data handling will be described in the statistical analysis plan (SAP).

9.4.3. Analysis of PUL Parameters, Pinch and Grip Strength, Brooke Scale

Change from baseline to Week 104 in hand/arm function and strength will be analyzed. In order to evaluate overall effect, composite scores may be explored. Two-sided 95% confidence intervals will be presented.

9.4.4. Analysis of LVEF, Cardiac Fibrosis, and Muscle Fat and Fibrosis

Changes from baseline in LVEF, cardiac fibrosis, and muscle fat and fibrosis will be summarized descriptively based on available data at Week 104.

9.4.5. Analysis of PODCI Quality Outcome Data

Changes from baseline in modified PODCI scores of subjects will be summarized descriptively based on available data at each assessment time point.

9.4.6. Pharmacokinetic Analyses

Pamrevlumab concentrations and derived PK parameters (including Cmin, Cmax, AUCtau, and t1/2) will be summarized using descriptive statistics. Pharmacokinetic analysis will be performed using commercial software such as WinNonlin.

Descriptive statistics (number of subjects, mean, geometric mean, standard deviation, minimum, maximum, and coefficient of variation) will be presented for the PK parameters (1) in the overall population, (2) in subjects 12 to 16 years of age, and (3) in subjects older than 16 years. Comparison of PK parameters between the age groups will be performed. Trough values, measured at several time points during the course of the study, will be compared to determine steady state and accumulation.

9.4.7. Safety Analyses

Safety analyses will include summary of adverse events, prior and concomitant medication use, measurements of laboratory tests, vital signs, and electrocardiograms (ECGs). In general, safety data will only be summarized descriptively and no inferential statistical procedures will be applied.

For data summarization, adverse events will be classified into standard terminology using a coding thesaurus (MedDRA), and reported by system organ class and preferred term.

Treatment-emergent adverse events will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Deaths, SAEs, and AEs leading to study or treatment discontinuation, and infusion reactions will be listed or tabulated separately.

Clinically significant changes from baseline in vital signs, laboratory tests, and ECG will be identified. Shift tables will summarize changes in selected laboratory measures.

All safety analyses will be performed based on the Safety Population.

9.5. Administrative Analyses

In this open-label exploratory study, safety will be monitored on an ongoing basis.

The DMC will review all safety data, which may include available pharmacokinetic data, and pulmonary function tests.

10. DIRECT ACCESS TO SOURCE DOCUMENTS

Following site prequalification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the International Conference on Harmonisation (ICH) E6 guideline.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IVRS [or IWRS], clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The investigator must also permit the U.S. FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the investigator is notified of an inspection pertaining to this study by the U.S. FDA or other applicable regulatory authorities, the investigator must notify FibroGen immediately.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents

11.2. Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, an independent ethics committee (IEC) or an institutional review board (IRB) may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

12. ETHICS

12.1. Ethical Considerations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) regulations, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or independent ethics committee (IEC) requirements.

12.2. Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The investigator is responsible for obtaining reapproval by the IRB/IEC annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

12.3. Informed Consent Form

No study procedure may be implemented prior to obtaining a signed, written Informed Consent (ICF) and/or Assent Form from the subject or written Informed Consent Form signed by the subject's legally authorized representative, as applicable. IRB review and approval are required for the ICF. The final IRB/IEC approved ICF must be provided to FibroGen for regulatory purposes.

If there are any changes to the Sample ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF.

Guidance for Clinical Teams: For studies conducted in the United States, each subject must provide his or her consent for the use and disclosure of personal health information under the U.S. Health Insurance Portability and Accountability Act (HIPAA) regulations by signing a

HIPAA Authorization Form. The HIPAA Authorization Form may be part of the ICF or may be a separate document. IRB review may or may not be required for the HIPAA Authorization Form according to study site policies.

12.4. Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and HIPAA.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent and HIPAA Authorization Form or separate authorization to use and disclose personal health information signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

13. DATA HANDLING AND RECORD KEEPING

13.1. Source Documents

Source documents are original documents, data, and records that are relevant to the clinical study. The investigator will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the CRFs/eCRFs and resolved queries.

13.2. Data Collection, Handling, and Verification

All required data will either be entered onto CRFs/eCRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with a full audit trail.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion, ensuring that all data is verifiable with source documents.

14. PUBLICATION POLICY

A detailed explanation of FibroGen's publication policy is described in the Clinical Trial Agreement.

15. REFERENCES

Au CG, Butler TL, Sherwood MC, Egan JR, North KN, Winlaw DS (2011) Increased connective tissue growth factor associated with cardiac fibrosis in the mdx mouse model of dystrophic cardiomyopathy. Int J Exp Pathol 92: (1):57-65

Bushby K, Finkel R, Birnkrant DJ, et al. (2010) Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 9: (1):77-93

Desguerre I, Mayer M, Leturcq F, Barbet JP, Gherardi RK, Christov C (2009) Endomysial fibrosis in Duchenne muscular dystrophy: a marker of poor outcome associated with macrophage alternative activation. J Neuropathol Exp Neurol 68: (7):762-773

Emery AE (1991) Population frequencies of inherited neuromuscular diseases--a world survey. Neuromuscul Disord 1: (1):19-29

Kharraz Y, Guerra J, Pessina P, Serrano AL, Munoz-Canoves P (2014) Understanding the process of fibrosis in Duchenne muscular dystrophy. Biomed Res Int 2014:965631

Mayer OH, Finkel RS, Rummey C, et al. (2015) Characterization of pulmonary function in Duchenne Muscular Dystrophy. Pediatr Pulmonol 50: (5):487-494

McKim DA, Katz SL, Barrowman N, Ni A, LeBlanc C (2012) Lung volume recruitment slows pulmonary function decline in Duchenne muscular dystrophy. Archives of Physical Medicine and Rehabilitation 93: (7):1117-1122

Miller MR, Hankinson J, Brusasco V, et al. (2005) Standardisation of spirometry. Eur Respir J 26: (2):319-338

Morales MG, Cabello-Verrugio C, Santander C, Cabrera D, Goldschmeding R, Brandan E (2011) CTGF/CCN-2 over-expression can directly induce features of skeletal muscle dystrophy. J Pathol 225: (4):490-501

Morales MG, Gutierrez J, Cabello-Verrugio C, et al. (2013) Reducing CTGF/CCN2 slows down mdx muscle dystrophy and improves cell therapy. Hum Mol Genet 22: (24):4938-4951

Pessina P, Cabrera D, Morales MG, et al. (2014) Novel and optimized strategies for inducing fibrosis in vivo: Focus on Duchenne Muscular Dystrophy. Skelet Muscle 4:7

Phillips MF, Quinlivan RC, Edwards RH, Calverley PM (2001) Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med 164: (12):2191-2194

Schram G, Fournier A, Leduc H, et al. (2013) All-cause mortality and cardiovascular outcomes with prophylactic steroid therapy in Duchenne muscular dystrophy. J Am Coll Cardiol 61: (9):948-954

Sun G, Haginoya K, Wu Y, et al. (2008) Connective tissue growth factor is overexpressed in muscles of human muscular dystrophy. J Neurol Sci 267: (1-2):48-56

Tandon A, Villa CR, Hor KN, et al. (2015) Myocardial fibrosis burden predicts left ventricular ejection fraction and is associated with age and steroid treatment duration in duchenne muscular dystrophy. J Am Heart Assoc 4: (4):e001338

Tangsrud SE, Carlsen KC, Lund-Petersen I, Carlsen KH (2001) Lung function measurements in young children with spinal muscle atrophy; a cross sectional survey on the effect of position and bracing. Arch Dis Child 84: (6):521-524

Vial C, Zuniga LM, Cabello-Verrugio C, Canon P, Fadic R, Brandan E (2008) Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. Journal of Cellular Physiology 215: (2):410-421

16. APPENDICES

APPENDIX 1. SCHEDULE OF ASSESSMENTS: SCREENING PERIOD THROUGH WEEK 26

Assessment[a]	Screening Period (4 Weeks)	Treatment Period (Weeks)													
		Day 0	2	4	6	8	10	12	14	16	18	20	22	24	26
Informed Consent & Assent	X														
Inclusion/ Exclusion	X														
Demographics	X														
Medical History	X														
Clinical laboratory assessments[b,1]	X			X		X		X						X	
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X							X						X	
Electrocardiogram	X														
Physical Examination[e]	X	X						X						X	
Muscle function tests[f]	X	X						X						X	
Pulmonary function tests[g]	X	X						X						X	
Cardiac MRI[i]	X[i]														
Muscle MRI[i]	X[i]														
Specialty labs[h]		X	X												X
Pamrevlumab infusion		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire		X													X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting BP, temperature) to be collected at every visit, and pre-infusion, within 15 minutes of completion, and within 15 minutes of completing observation period.
d. Weight and height (estimated from ulna length) to be measured at screening and every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at screening. Other exams may be disease specific or problem oriented.
f. Muscle function tests (MFT): Brooke Scale, Performance of Upper Limb, Pinch Test, and Grip Test. MFTs will be performed during the screening period. MFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
g. Pulmonary function tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow. PFTs will be performed during the screening period. PFTs will be repeated on Day 0 (start of dosing) or at any time up to and including the Week 2 visit. The results from both time points will be used to establish baseline values.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Baseline muscle MRI may be conducted during the screening period or up to Week 4 dosing visit. Local safety labs are required prior to the MRIs, and must include hematocrit.

APPENDIX 2. SCHEDULE OF ASSESSMENTS: WEEK 28 THROUGH WEEK 58

Assessment[a]	Treatment Period (Weeks)													
	28	30	32	34	36	38	40	42	44	46	48	50	52	54,56, 58
Clinical laboratory assessments[b,i]					X						X			
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]					X						X			
Electrocardiogram													X	
Physical Examination[e]					X						X			
Muscle function tests[f]					X						X			
Pulmonary function tests[g]					X						X			
Cardiac MRI[i]													X	
Muscle MRI[i]													X	
Specialty labs[h]													X	
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire													X	

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured at screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 48. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs are required prior to the MRIs and must include hematocrit.

APPENDIX 3. SCHEDULE OF ASSESSMENTS: WEEK 60 THROUGH WEEK 104

Assessment[a]	Treatment Period (Weeks)								
	60	62,64, 66,68,70	72	74,76, 78,80,82	84	86,88,90, 92,94	96	98,100,102	104
Clinical laboratory assessments[b,i]	X		X		X		X		
Vital Signs[c]	X	X	X	X	X	X	X	X	X
Weight/Height[d]	X		X		X		X		
Electrocardiogram									X
Physical Examination[e]	X		X		X				X
Muscle function tests[f]	X		X		X				X
Pulmonary function tests[g]	X		X		X				X
Cardiac MRI[i]									X
Muscle MRI[i]									X
Specialty labs[h]									X
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X
Adverse Events & Concomitant Medications	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire									X

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.
d. Weight and height (estimated from ulna length) to be measured in screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 104. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Appendix 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs required prior to the MRIs and must include hematocrit.

APPENDIX 4. SCHEDULE OF ASSESSMENTS: WEEK 106 THROUGH WEEK 210/EOS

Assessment[a]	Treatment Period (Weeks)										Safety Follow-up
	106, 108, 110, 112, 114	116	118, 120, 122, 124, 126	128	130, 132, 134, 136, 138	140	142, 144, 146, 148, 150	152	154	156	210/ EOS
	158, 160, 162, 164, 166	168	170, 172, 174, 176, 178	180	182, 184, 186, 188, 190	192	194, 196, 198, 200, 202	204	206	208/EOT	
Clinical laboratory assessments[b,i]		X		X		X		X			X
Vital Signs[c]	X	X	X	X	X	X	X	X	X	X	X
Weight/Height[d]		X		X		X		X			
Electrocardiogram										X	
Physical Examination[e]		X		X		X				X	
Muscle function tests[f]		X		X		X				X	
Pulmonary function tests[g]		X		X		X				X	
Cardiac MRI[i]										X	
Muscle MRI[i]										X	
Specialty labs[h]										X	X
Pamrevlumab infusion	X	X	X	X	X	X	X	X	X	X[j]	
Adverse Events & Concomitant	X	X	X	X	X	X	X	X	X	X	X
PODCI Quality Outcome Questionnaire										X	

Abbreviations: MRI, magnetic resonance imaging; PODCI, Pediatrics Outcomes Data Collection Instrument

a. See Section 7 for details on approved windows, assessments and dosing.
b. Safety labs: See Section 7.2.7.1. Central labs are required at visits noted in this table.
c. Vital signs (pulse, respiration, sitting blood pressure, and temperature) to be collected at every visit, and pre-infusion, within 15 minutes of infusion completion and within 15 minutes of completing the observation period.

d. Weight and height (estimated from ulna length) to be measured in screening and approximately every 3 months thereafter.
e. Physical exam to include assessment of subject's ventilation use. A complete exam is required at Week 208/EOT. Other exams may be disease specific or problem oriented.
f. Muscle function tests: Brooke Scale, Performance of Upper Limb, Pinch Strength Test, and Grip Test.
g. Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, maximal inspiratory pressure, maximum expiratory pressure, peak expiratory flow rate, peak cough flow.
h. See Section 5 for pharmacokinetic/human antihuman antibody/connective tissue growth factor and Exploratory Sample collection details.
i. Local safety labs required prior to the MRIs and must include hematocrit.
j. Pamrevlumab infusion is administered at Week 156, but is NOT to be administered at week 208/EOT.

APPENDIX 5. SPECIALTY LAB SCHEDULE

		Treatment Period									Safety Follow-up
Sample	**Timepoint**	**Day 0**	**Day 2 ±1 day**	**Day 4 ±1 day**	**Day 7 ±1 day**	**Day 10±1 day**	**Week 2**	**Week 26**	**Week 52**	**Week 104, 156, 208 /EOT**	**Week 210/EOS (4 wks post last dose)**
Pamrevlumab Pk[a]	Before infusion	X					X	X	X		
	Within 1 hour after infusion	X							X		
	Time point sample (no infusion)		X	X	X	X					
HAHA[b]	Predose (when applicable)	X									X
CTGF[c]	Predose (when applicable)	X								X	
Exploratory[d]	Predose (when applicable)	X							X	X	

Abbreviations: CTGF = connective tissue growth factor; ET = early termination; HAHA = human anti-human antibody; PK = pharmacokinetic

a. Approximately 1-2 mL of blood will be collected for each measurement of pamrevlumab PK.

b. Approximately 1 mL of blood will be collected for each measurement of HAHA.

c. Blood and urine samples will be collected. Approximately 1 mL of blood and 0.5 mL of urine will be collected for each measurement of CTGF.

d. Approximately 5 mL of blood will be collected for each exploratory sample.

APPENDIX 6. OPEN LABEL EXTENSION (OLE)

This is an open-label, single arm extension to evaluate long-term efficacy and safety of pamrevlumab in DMD subjects who have been previously treated with pamrevlumab. Each subject will receive pamrevlumab (35 mg/kg) intravenously, every 2 weeks for up to 208 weeks.

Upon completion of the trial, subjects will be asked to return to the investigative site to complete final safety and efficacy assessments with an End of Study Visit.

See parent study protocol for detailed information on study drug formulation, storage, and administration.

1. ENDPOINTS

Cardiac assessments:

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

Pulmonary assessment:

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

Muscles Fibrosis assessments:

- Annual mean change in fibrosis score of the biceps brachii, assessed by MRI.
- Annual mean change in fibrosis score of the Respiratory Muscles (Chest wall & Diaphragm), assessed by MRI.

Performance assessments:

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

Safety Assessments:

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

2. STUDY ENROLLMENT

All subjects participating in the Open Label Extension must have completed treatment through the primary endpoint and completed the EOT visit on the parent pamrevlumab DMD study. The study investigator must consider the subject medically stable for continued treatment. Written consent/assent by the subject and/or their legal guardian (as required by the site's IRB) must be obtained prior to the subject's participation in the OLE.

3. STUDY VISITS

All study visits will be performed in accordance with the Schedule of Assessments presented in Section 6.

The dosing period begins on the first day of dosing with study treatment (Day 0), which is to be conducted simultaneously with, or within 7 days after the parent study EOT visit. The dosing period continues until Week 208/EOT. Subjects will receive study drug every 2 weeks. The visit window for these visits is ±3 days. Each visit should be scheduled based on the previous visit, not the Day 0 (baseline) visit.

Muscle or pulmonary function tests that cannot be performed or produce inadequate results according to test procedures during a specified visit should be performed by the next scheduled dosing visit.

Cardiac, muscle, and Respiratory Muscles and Diaphragm MRIs may be performed within ±2 weeks of the specified visit.

Subjects who complete the dosing period must have their end of treatment assessments performed at the Week 208/EOT visit. The end of treatment Cardiac, Muscle, and Respiratory Muscles and Diaphragm MRIs may be performed any time from Week 208/EOT to Week 210/EOS/ET (End of Study / Early Termination) visit.

Subjects who prematurely discontinue the study will be strongly encouraged to complete the final efficacy evaluations scheduled for Week 208/EOT as applicable, and the safety follow-up evaluations scheduled for the Week 210/EOS/ET visit (4 weeks following the last dose).

For all subjects, the final safety assessments should be completed at the Week 210/EOS/ET visit, 4 weeks (±7 days) after the last dose of pamrevlumab.

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

3.1. Home Health Care

FibroGen may consider the use of properly trained home health care staff to administer the pamrevlumab infusions in the future and corresponding study assessments during the conduct of the study, consistent with institutional regulations and policies. Home Health Care (HHC) is optional and the decision to utilize is driven by the site. Subjects who experience a significant infusion reaction will not be allowed to participate in HHC. Medications for the treatment of acute reactions, including anaphylaxis, will accompany the HHC nurse. HHC support will only

be on weeks where no PFT, MFT, safety lab collection, or MRI are being conducted, but only a study drug infusion is occurring.

4. STUDY ASSESSMENTS

All study assessments will be performed in accordance with the Schedule of Assessments presented in Section 6. Refer to the Laboratory Manual for details regarding laboratory sample collection and processing; and the Study Reference Manual for details regarding the conduct of functional tests and MRIs.

Pulmonary function tests (PFTs) will be performed to assess changes in lung function: forced vital capacity (FVC), and peak expiratory flow rate (PEF; PEFR), and forced expiratory volume in 1 second (FEV1).

Performance of the Upper Limb (PUL), and Grip Tests will be performed to assess changes in upper extremity strength and function.

Imaging assessments will be performed to assess changes in muscle fibrosis: Cardiac, upper arm muscle, respiratory muscles and diaphragm MRIs.

A full physical examination will be performed approximately every 10 weeks.

Vital signs (pulse, respiratory rate, sitting blood pressure, and temperature) will be collected at all visits. During infusion visits, vital signs will be collected prior to start of each infusion, within 15 minutes of the end of each infusion, and within 15 minutes of the completion of the post-infusion observation period.

All laboratory tests will be performed at a central laboratory according to the Schedule of Assessments in Section 6. A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local clinical laboratories will be used to assess and facilitate the management of adverse events and to provide usual standard of care (including blood draws required prior to MRIs). Local clinical laboratory data will not be collected in the study database except for hematocrit values provided with imaging data.

Safety labs will be drawn at the site's local lab prior to MRIs to ensure there is no contraindication to MRI. Hematocrit should be included in the local lab draw as these results are required to assess fibrosis and will be provided to the central imaging vendor along with the MRI scans. Details are included in the Imaging Manual.

5. STATISTICAL CONSIDERATIONS

Data collected during the extension period will be summarized descriptively along with the main study.

6. OLE SCHEDULE OF ASSESSMENTS: EX – DAY 0 THROUGH EX – WEEK 210/EOS/ET

	Treatment Period [a]					Follow Up Period
	Day 0 [b]	Q2 WEEKS: ALL VISITS through Week 206	Q12 weeks through Week 204 (Wk 12, 24, 36, etc.)	Q52 weeks through Week 156 (Wk 52, 104, 156)	Week 208/EOT	Wk 210/ EOS/ET [p]
Informed Consent & Assent	x					
Eligibility Assessment	x					
Vital Signs [c]	x	x	x	x	x	x
Chemistry & Hematology			x			x
PFT / Height (ulna length) [f,h,i]			x			x[q]
Muscle Function Tests [f,g]			x			x[q]
Physical Examination [k]			x			x
Weight [j]	x		x			
Weight Based Dose Adjustment [j]	x		x			
ECG [f]				x	x	x[q]
Cardiac, Muscle, Respiratory Muscles and Diaphragm MRIs [d,e,f]				x	x	x[q]
Specialty Labs [o]	x			x	x	x
Pamrevlumab Infusion [l]	x	x	x	x		
AEs / SAEs [m]	x	x	x	x	x	x
Concomitant Medications [n]	x	x	x	x	x	x

Abbreviations: AE = adverse event; ECG = electrocardiogram; ET= Early Termination; ICF = Informed Consent Form; PFTs = Pulmonary Function Test;

a.) Visit window of ± 3 days starting at Week 2.
b.) Day 0 to be conducted simultaneously with, or within 7 days after the parent study EOT visit.
c.) Vital signs (pulse, respiration, sitting BP, temperature) to be collected at every visit: pre-infusion, and within 15 minutes of completion, and within 15 minutes of completing the observation period.

d.) Local safety labs are required prior to MRIs and must include hematocrit.
e.) Cardiac, muscle, and Respiratory Muscles and Diaphragm MRIs may be performed within ±2 weeks of the specified visit
f.) PFTs, MFTs, MRIs, and ECG do not require repetition if performed within 4 weeks.
g.) For Non-ambulatory subjects only: Muscle Function Tests (MFTs): Performance of Upper Limb, and Grip Test.
h.) Pulmonary Function Tests (PFTs): forced vital capacity, forced expiratory volume in 1 second, peak expiratory flow rate.
i.) Height will be measured at each PFT interval using ulna length to approximate standing height.
j.) Weight will be measured at Screening and every 12 weeks thereafter to determine dose for the subsequent 12-week interval. Weight is collected during the dose adjustment visit or up to two weeks in advance.
k.) Full physical exam including chest auscultation
l.) Pamrevlumab infusion is NOT to be administered at week 208 (EOT)
m.) AEs and SAEs are collected from date of consent through EOS.
n.) Concomitant medications and nondrug therapies must be reported beginning after informed consent is obtained and ends 30 days after the last treatment.
o.) Specialty labs for HAHA (human anti-human antibody
p.) Subjects who terminate prior to Week 208/EOT should complete the Early Termination (ET) visit.
q.) Assessment required only if subject terminated study prior to Week 208