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 7903 and 7913)
AMENDMENT 7.0:	27 September 2019
AMENDMENT 8.0	18 November 2020

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

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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 7903 and 7913)

Amendment 7.0: 27 September 2019

Amendment 8.0: 18 November 2020

This protocol is approved by FibroGen.

[redacted]

08-Dec-20 | 13:12:12 PST

Date

[redacted], FibroGen, Inc.

AMENDMENT 8.0: 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
Safety follow-up extended to 60 days (+3 days) after the last infusion	To align with safety follow-up of 5 times half-life of Pamrevlumab of 12.2 days	Section 7.1.5, 8.3.1, and Appendix 6: OLE
Removed Upper Arm Muscle MRI and Respiratory Muscles and Diaphragm MRI and associated endpoints from OLE.	Changes in Fibrosis/MRI endpoints are not a direct measure of patient function and are of uncertain clinical meaningfulness as a biomarker of disease progression. Therefore, Fibrosis/MRI endpoints will only be in the main study, and only Cardiac MRI will be conducted in the OLE. Respiratory Muscles and Diaphragm MRI is not a direct measure of pulmonary function, which is measured on this study through spirometry to reflect the impact of pamrevlumab on pulmonary function.	Section 7.1.2, and Appendix 6: OLE
IP administration window time updated from 24 to 48 hours	To align with updated stability information for Pamrevlumab	Section 6.1.4
ECGs removed	To align with standard of care	Appendix 6: OLE
Provide further clarity on the overall duration of the Open Label Extension.	For better readability and clarity on the length of the OLE	Appendix 6: OLE
Modified open label extension assessments including labs, PFTs and physical exams	To align further with standard of care for improved implementation	Appendix 6: OLE

Provide allowance for administration of approved DMD therapies during the OLE treatment period >3hours after pamrevlumab administration	To allow administration of approved DMD therapies during the OLE treatment period	Synopsis, Appendix 6: OLE

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 8.0
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 $t1/2$) [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 during the main study and allowed during the Open Label Extension at the discretion of the investigator. 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.

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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 48 hours of preparation and within 6 hours if left at room temperature after 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.

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 4 weeks (±7 days) after the last dose of pamrevlumab, and subjects will receive a final safety follow-up phone call 60 days (+ 3 days) after the last dose.

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 (Main Study)

Please refer to the Schedules of Assessments for the main study 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 and final safety follow-up phone call 60 days (+ 3 days) after the last dose.

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: 1-215-616-3096-Email: FibroGen_SAEs@iconplc.com

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

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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	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 until the last subject from the phase 3 DMD program completes 52 weeks of treatment on OLE or when pamrevlumab is commercially available or when the Sponsor decides to end the study.

Upon completion of the trial, subjects will be asked to return to the investigative site 4 weeks after their last treatment visit to complete final safety and efficacy assessments with an End of Study Visit, and will receive a final safety follow-up phone call 60 days (+ 3 days) after the last dose.

See parent study protocol for detailed information on study drug formulation, storage, and administration.

1. Endpoint

Pulmonary assessment:

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

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).

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.

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. Administration of current approved DMD therapies is allowed during the OLE treatment period if deemed acceptable by the investigator. Administration of such therapies must be withheld for three hours after the end of pamrevlumab infusion.

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 the last subject from the phase 3 DMD program completes 52 weeks of treatment on OLE or when pamrevlumab is commercially available or when the Sponsor decides to end the study. 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 MRI 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 MRI 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) and a final safety follow-up phone call 60 days (+3 days) after the last dose of pamrevlumab as per the schedule of assessments..

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 and a final safety follow-up phone call 60 days (+3 days) after the last dose of pamrevlumab as per the schedule of assessments.

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 Cardiac muscle fibrosis.

A full physical examination will be performed approximately every 24 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.)	Q24 Weeks (Wk 24, 48, 72, etc.)	Q52 weeks through Week 156 (Wk 52, 104, 156, 208[r]/EOT)	Wk 210/ EOS/ET [p]	Final Safety phone call 60 Days (+3 days) after last treatment
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		x[q]	
Physical Examination [k]				x		x	
Weight [j]	x		x	x			
Weight Based Dose Adjustment [j]	x		x	x			
Cardiac MRI [d,e,f]					x	x[q]	
Specialty Labs [o]	x					x	
Pamrevlumab Infusion [l]	x	x	x	x	x		
AEs / SAEs [m]	x	x	x	x	x	x	x
Concomitant Medications [n]	x	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 MRI may be performed within ±2 weeks of the specified visit
f.) PFTs, MFTs, and MRI 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 until subject reaches adult height. Adult height will be carried forward.
j.) Weight will be measured every 12 weeks 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) / Neutralizing 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
r.) 208 weeks is an estimation of maximum duration for OLE. Actual duration of the OLE will be determined at the Sponsor's program level.