# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| **STUDY TITLE:** | A Phase 3, Randomized, Double-Blind, Trial of Pamrevlumab (FG-3019) or Placebo in Combination with Systemic Corticosteroids in ambulatory subjects with Duchenne Muscular Dystrophy (DMD) |
| **PROTOCOL NUMBER:** | FGCL-3019-094 |
| **PHASE:** | Phase 3 |
| **STUDY SPONSOR:** | FibroGen, Inc.<br>409 Illinois Street<br>San Francisco, California 94158 USA |
| **KEY SPONSOR CONTACT(S):** | Name: [redacted]<br>Title: [redacted]<br>Mobile: [redacted]<br>E-mail Address: [redacted] |
| **EUDRACT NUMBER:** | 2020-000699-39 |
| **IND NUMBER:** | 126630 |
| **STUDY DRUG:** | Pamrevlumab (FG-3019) |
| **INDICATION:** | Duchenne Muscular Dystrophy |
| **ORIGINAL PROTOCOL:** | 30 April 2020 |
| **Amendment 1:** | 12 October 2020 |
| **Amendment 2:** | 26 October 2020 |
| **Amendment 3:** | 09 August 2021 |
| **Amendment 4:** | 28 October 2022 |

# INVESTIGATOR SIGNATURE PAGE

## STUDY ACKNOWLEDGEMENT

A Phase 3, Randomized, Double-Blind, Trial of Pamrevlumab (FG-3019) or Placebo in Combination with Systemic Corticosteroids in Ambulatory Subjects with Duchenne Muscular Dystrophy (DMD)

**FGCL-3019-094**

Original: 30 April 2020

Amendment 1: 12 October 2020

Amendment 2: 26 October 2020

Amendment 3: 09 August 2021

Amendment 4: 28 October 2022

## 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, and any applicable local health authority, and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements.

| | | |
|---|---|---|
| | | |
| Investigator Name (Printed) | | Institution |
| | | |
| Signature | | Date |

Please return a copy of this signature page to FibroGen (or designee). Please retain the original for your study files.

# CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 30 April 2020

Amendment 1: 12 October 2020

Amendment 2: 26 October 2020

Amendment 3: 09 August 2021

Amendment 4: 28 October 2022

This protocol is approved by FibroGen.

| | | |
|---|---|---|
| [redacted]<br>FibroGen, Inc. | | Date |

*See appended final page for 21CFR Part 11 compliant approval

## AMENDMENT 4.0: KEY CHANGES

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 |
|---|---|---|
| In addition to the changes listed below, minor editorial changes were made throughout the document to improve consistency and clarity | To correct typographical errors, and to improve consistency and clarity | Throughout the document |
| Removed "linearized" from NorthStar Ambulatory Assessment (NSAA) score | The scoring of the NSAA will be clarified in the SAP | Throughout the document |
| Removed preliminary FGCL-3019-079 data | Completed FGCL-3019-079 study results available and presented in last IB | Section 2.5, Section 2.6 |
| Added bone fracture and height velocity safety assessments | To align with the pediatric investigational plan | Synopsis, Section 3.2.3, Appendix 1 Schedule of Assessments, Appendix 4 |
| Removed portion of inclusion criteria "Received pneumococcal vaccine (PPSV23) (or any other pneumococcal polysaccharide vaccine as per national recommendations) prior to study entry."<br>Modified this eligibility criteria into a recommendation instead of a requirement. Inserted language on vaccine recommendations for DMD patients based on national guidance. | Vaccine recommendations vary by country and also depend on patient health status. Due to this, FibroGen recommends patients be fully vaccinated against pneumococcal bacteria and influenza based on standard of care and national guidance, age and health status but does not enforce the requirement through eligibility criteria, nor which type of vaccine is required. | Synopsis, Section 4.1, 6.1.1 |

| | | |
|---|---|---|
| Removed exclusion criteria "hypersensitivity reaction to Gadolinium-based Contracts Agents (GBCA) required for MRI acquisition." In addition, removed language pertaining to contract MRI.<br><br>Prior to MRI, local laboratory assessments may be drawn at the discretion of the investigator. The results of any local laboratory assessments are used to evaluate if it is safe for the subject to undergo the MRI with contrast. These local laboratory results will not be captured in the clinical database | Requirement for contrast MRI pertains only to the cardiac MRI which was removed in Protocol Amendment 3 | Synopsis, Section 4.2, 6.2.3.1, |
| Removed Genomics from specialty labs | Clarification that Genomics is not collected in this study | Schedule of Assessments |
| Language regarding the end of infusion was added | To clarify that the end of infusion is when the IP bag is empty. Post-flush is not included | Section 5.1.6 |
| Clarified that medications for treatment of acute reactions, including anaphylaxis, are stored in a lockbox in the patient's home for access by the Home Health Care nurse. | Further clarification regarding the location of home health care medications | Section 5.1.6, 5.1.7 |
| Removed language regarding destruction of partially used IP | Used/partially used IP will be destroyed in reconstitution. | Section 5.1.9 |
| Added language on where the COVID vaccinations should be captured in EDC | Added for clarity on where vaccinations should be captured in EDC. | Section 5.2.1 |
| Added preliminary non-clinical study results | Preliminary results of rabbit embryo-fetal development study available to inform contraception recommendations | Section 5.2.3 |

| | | |
|---|---|---|
| Collection of specific genetic DMD mutation | To support characterization of most recent DMD mutation landscape and potentially evaluate possible relationships between patient genotype and clinical outcomes | Section 6.1.1 |
| Added language regarding missed PFT and MFT assessments | Added for clarity that missed PFT or MFTs should be conducted at the next scheduled visit or sooner if feasible. | Section 6.1.4, 6.2.4 |
| Glomerular Filtration Rate (GFR) calculation language added | Clarification that GFR is resulted by the central lab and the calculation that is used. | Section 6.2.3.1 |
| Clarified height is collected at screening and Unscheduled visits and added height collection at Week 52. | Clarification added for assessments collected during vital signs examination at screening; height collection added for assessment of growth velocity | Section 6.2.2 |
| Clarified videos of performance assessments will be sent for QC at certain visit weeks as well as when needed if required due to quality issues | Added for clarity to further describe the on-going process functional testing quality control. | Section 6.2.6 |
| LVEF% removed | LVEF% capture pertains only to the cardiac MRI which was removed in Protocol Amendment 3 | Section 6.2.8.1 |
| Clarified China will not perform DMD video assessments | Due to Regulatory guidelines this assessment will not be performed in China | Section 6.2.8.2 |
| Additional PK, HAHA, HAHA-NA and immunogenic reaction blood draws | To meet Regulatory recommendations for immunogenicity testing and to include local guidance to be followed for total blood volume. | Section 6.2.3.1, 6.2.4.3, Appendix 2, Appendix 3 |
| Effect size, treatment difference, and common standard deviation revised in the Sample Size sections | Numbers revised to reflect both the raw and linearized scales | Synopsis, Section 8.1 |

| | | |
|---|---|---|
| Language added to Efficacy Analyses sections | To further clarify the analyses to be used | Sections 8.3.4.1, 8.3.4.2, 8.3.4.2.4, and 8.3.4.2.5.1 |
| Language added regarding ATOM video QC | Added to clarify the data collection, handling, and verification of video QC of the MFTs by study vendor ATOM | Section 11.3, Section 6.2.6 |
| Removed "Weight" footnote as it already has a row in the SoA and added "Height" to the SoA | For added clarity | Appendix 1 Schedule of Assessments, Appendix 4 OLE Schedule of Assessments |
| Added clarification on starting week for patients entering the Open Label Extension portion of the trial and when End of Study visit takes place | For added clarity | Appendix 4 Open Label Extension |
| Added timeframe of "within an 8 week period" to the OLE missed doses language. | To align with the main study | Appendix 4 Open Label Extension |
| Removed "Annual mean" from Ambulatory functional assessments | To update the OLE endpoints | Appendix 4 Open Label Extension |

# TABLE OF CONTENTS

## LIST OF TABLES



## LIST OF FIGURES

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| 4SCV | 4-stair climb Velocity |
| 6MWD | 6-minute walking distance |
| ADA | anti-drug antibody |
| AE | adverse event |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ANCOVA | analysis of covariance model |
| ANCOVA-MI | analysis of covariance model with Multiple Imputations |
| AST | aspartate aminotransferase |
| AUC | Area under the curve |
| BMP | bone morphogenetic protein |
| BP | Blood pressure |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| CCN | cellular communication network |
| CMR | cardiovascular magnetic resonance |
| CNS | central nervous system |
| CPAP | continuous positive airway pressure |
| CRF | case report form |
| CRP | C-reactive protein |
| CS | clinically significant |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTGF | connective tissue growth factor |
| DCM | dilated cardiomyopathy |
| DMC | Data Monitoring Committee |
| DMD | Duchenne Muscular Dystrophy |
| DN | diabetic nephropathy |
| ECG | electrocardiogram |
| ECM | extracellular matrix |

| Abbreviation | Definition |
|---|---|
| EDC | electronic data capture |
| EMT | epithelial mesenchymal transformation |
| EOS | End of Study |
| ET | Early Termination |
| FEV1 | forced expiratory volume at 1 second |
| FSGS | focal segmental glomerulosclerosis |
| FVC | forced vital capacity |
| GCP | Good Clinical Practice |
| GCS | Global Circumferential Strain |
| GFR | Glomerular filtration rate |
| GGT | gamma glutamyl transferase |
| HAHA | Human Anti-Human Antibody |
| HHC | Home Health Care |
| HHM | Hand Held Myometry |
| HIPAA | Health Insurance Portability and Accountability Act |
| HSPG | heparan sulfate proteoglycan |
| IB | Investigator's Brochure |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IgG | immunoglobulin G1 |
| IP | investigational product |
| IRB | Institutional Review Board |
| ITT | Intent to Treat |
| IXRS | Interactive Response System |
| LF | Liver fibrosis |
| LGE | Late Gadolinium Enhancement |
| LoA | Loss of Ambulation |
| LRP | Lipoprotein receptor-related protein |
| LVEF | Left ventricular ejection fraction |
| LVEF % | Left Ventricular Ejection Fraction percentage |

| Abbreviation | Definition |
|---|---|
| MAR | Missing at random |
| MNAR | Missing not at random |
| MRI | Magnetic resonance imaging |
| NCI | National Cancer Institute |
| NCS | not clinically significant |
| NSAID | nonsteroidal anti-inflammatory drug |
| OLE | open-label, extension treatment |
| OTC | over-the-counter |
| PDAC | Pancreatic ductal adenocarcinoma |
| PFT | pulmonary function test |
| PK/PD | pharmacokinetics/pharmacodynamics |
| PP | Per protocol |
| ppFVC | percent predicted forced vital capacity |
| ppPEF | percent predicted peak expiratory flow |
| PUL | Performance of Upper Limb |
| RBC | red blood cell |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SOA | Schedule of Assessment |
| SPARC | secreted protein acidic and rich in cysteine |
| TEAE | treatment-emergent adverse event |
| TESAE | treatment-emergent serious adverse event |
| TTSTAND | Time to stand |
| ULN | upper limit of normal |
| WBC | white blood cells |
| WHODrug | World Health Organization Drug |

# 1. PROTOCOL SYNOPSIS

| | |
|---|---|
| Study Title: | A Phase 3, Randomized, Double-Blind, Trial of Pamrevlumab (FG-3019) or Placebo in Combination with Systemic Corticosteroids in Ambulatory Subjects with Duchenne Muscular Dystrophy |
| Protocol Number: | FGCL-3019- 094 |
| Investigational Product: | Pamrevlumab (FG-3019) |
| Study Phase: | Phase 3 |
| Indication: | Duchenne Muscular Dystrophy |
| Number of Subjects Planned: | Approximately 70 |
| Number of Sites Planned: | Approximately 60 sites globally |

OBJECTIVES

Study Objective: To evaluate the efficacy and safety of pamrevlumab versus placebo in combination with systemic corticosteroids administered every two weeks in ambulatory subjects with Duchenne muscular dystrophy (age 6 to <12 years).

ENDPOINTS

**Primary Endpoint:**

Ambulatory functional assessment:

- Change in NorthStar Ambulatory Assessment (NSAA) total score from baseline to Week 52.

**Secondary Endpoints:**

Other Muscle function assessments:

- Change in 4-stair climb Velocity (4SCV) assessment from baseline to Week 52.
- Change in the 10-meter walk/run test from baseline to Week 52.
- Changes in Time to Stand (TTSTAND) from baseline to Week 52.
- Time to Loss of Ambulation (LoA) from baseline to Week 52

**Exploratory Endpoint:**

- Change in Duchenne Video Assessment severity percentage from baseline to Week 52.
- Change in ppFVC and ppPEF assessed by spirometry, from baseline to Week 52.

MRI Assessment:

- Changes in lower extremities vastus lateralis muscle fibrosis score from baseline to Week 52, assessed by MRI.

**Safety Assessments**

- All treatment emergent adverse events (TEAEs), serious adverse events (SAEs), clinically significant laboratory test abnormalities, discontinuation of treatment due to treatment-related AEs and hypersensitivity/anaphylactic reactions.
- Number and percentage of subjects with hospitalizations due to any serious adverse events with pulmonary and/or cardiac cause(s).
- Number and percentage of subjects with bone fractures
- Annualized height velocity, HV (cm/year) from Baseline to Week 52

**Pharmacokinetics/pharmacodynamics (PK/PD) assessment**

- Population PK/PD analysis.

STUDY DESIGN

This is a global, randomized, double-blind, trial of pamrevlumab or placebo in combination with systemic corticosteroids in subjects with Duchenne muscular dystrophy, aged 6 to <12 years (ambulatory subjects only). Approximately 70 subjects will be randomized at a 1:1 ratio to Arm A (pamrevlumab + systemic deflazacort or equivalent potency of corticosteroids administered orally) or Arm B (placebo+ systemic deflazacort or equivalent potency of corticosteroids administered orally), respectively.

| Arm A | Arm B |
|---|---|
| pamrevlumab 35 mg/kg IV Q2 weeks + systemic deflazacort or equivalent potency of corticosteroids administered orally | matching placebo IV Q2 weeks + systemic deflazacort or equivalent potency of corticosteroids administered orally |

- Randomization will be stratified by exon 44 deletion.

Subjects who complete 52 weeks of treatment may be eligible to enter into the open-label, extension treatment (OLE) with pamrevlumab + systemic corticosteroids

STUDY PERIODS

**Screening period:** Up to 4 weeks
**Treatment period:** 52 weeks (last dose on week 52)
**Efficacy Assessment Period (EAP):** At Week 52

Safety Follow-up period/End of Study (EOS): A visit 28 days (+/- 3 Days) and a final safety follow-up phone call 60 days (+ 3 Days) after the last dose

Open label Extension (Appendix 4): Continued treatment with pamrevlumab

**SUBJECT ELIGIBILITY CRITERIA**

**Key Inclusion Criteria**

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

**Age, and consent:**

1. Males at least 6 to <12 years of age at screening initiation
2. Written consent by patient and/legal guardian as per regional/country and/or IRB/IEC requirements

**DMD diagnosis:**

3. Medical history includes diagnosis of DMD and confirmed Duchenne mutation using a validated genetic test.

**Pulmonary criteria:**

4. Average (of Screening and Day 0) percent predicted FVC above 45%
5. On a stable dose of systemic corticosteroids for a minimum of 6 months, with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening. Corticosteroid dosage should be in compliance with the DMD Care Considerations Working Group recommendations (e.g. prednisone or prednisolone 0.75 mg/kg per day or deflazacort 0.9 mg/kg per day) or stable dose. A reasonable expectation is that dosage and dosing regimen would not change significantly for the duration of the study

**Performance criteria:**

6. Able to complete 6MWD test with a distance of at least 270M but no more than 450M on two occasions within 3 months prior to Randomization with ≤10% variation between these two tests.
7. Able to rise (TTSTAND) from floor in <10 seconds (without aids/orthoses) at screening visit.
8. Able to undergo MRI test for the lower extremities vastus lateralis muscle.

**Vaccination:**

9. Agreement to receive annual influenza vaccinations during the course of the study.

**Laboratory criteria:**

10. Adequate renal function: cystatin C ≤1.4 mg/L
11. Adequate hematology and electrolytes parameters:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /µL
    d. Serum calcium (Ca), potassium (K), sodium (Na), magnesium (Mg) and phosphorus (P) levels are within a clinically accepted range for DMD patients.
12. 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

**Key Exclusion Criteria**

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

**General Criteria:**

1. Concurrent illness other than DMD that can cause muscle weakness and/or impairment of motor function
2. Severe intellectual impairment (eg, severe autism, severe cognitive impairment, severe behavioral disturbances) preventing the ability to perform study assessments in the Investigator's judgment
3. Previous exposure to pamrevlumab
4. BMI ≥40 kg/m2 or weight >117 kg
5. History of:
   a. allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies
   b. hypersensitivity to study drug or any component of study drug
6. Exposure to any investigational drug (for DMD or not), in the 30 days prior to screening initiation or use of approved DMD therapies (e.g., eteplirsen (exondys 51), ataluren, golodirsen (vyondys 53), casimersen (amondys 45)) within 5 half-lives of screening, whichever is longer with the exception of the systemic corticosteroids, including deflazacort

**Pulmonary, Renal and Cardiac criteria:**

7. Requires ≥16 hours continuous ventilation
8. Poorly controlled asthma or underlying lung disease such as bronchitis, bronchiectasis, emphysema, recurrent pneumonia that in the opinion of the investigator might impact respiratory function
9. Hospitalization due to respiratory failure within the 8 weeks prior to screening
10. Severe uncontrolled heart failure (NYHA Classes III-IV), or renal dysfunction, including any of the following:
    a. Need for intravenous diuretics or inotropic support within 8 weeks prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia within 8 weeks prior to screening
    c. Patients with glomerular filtration rate (GFR) of less than 30 mL/min/1.73m2 or with other evidence of acute kidney injury as determined by investigator
11. Arrhythmia requiring anti-arrhythmic therapy
12. Any other evidence of clinically significant structural or functional heart abnormality

**Clinical judgment:**

13. The Investigator judges that the subject will be unable to fully participate in the study and complete it for any reason, including inability to comply with study procedures and treatment, or any other relevant medical, surgical or psychiatric conditions

**STUDY TREATMENT**

**Dose and Mode of Administration**

**Pamrevlumab (or placebo)**: 35 mg/kg IV, Day 0 and every 2 weeks thereafter with the last dose at week 52. Subjects will receive up to 27 infusions over the course of the main study.

**Systemic Corticosteroids**: Systemic deflazacort or equivalent potency of corticosteroids administered orally

**STATISTICAL METHODS**

**Sample Size Calculations:**

With a total sample size of 70 subjects allocated in a 1:1 ratio between the treatment arm and placebo, the study will achieve at least 80% power to detect an effect size of 0.705 (assuming a treatment difference of 6.0 points in linearized total NSAA with common standard deviation of 8.5, or a treatment difference of 1.91 in raw total NSAA with common standard deviation of 2.71) in the mean change from baseline in the total NSAA score with a one-sided significance level (alpha) of 0.025.

**Statistical Analysis Methods:**

The primary endpoint, change in the total score of NSAA, from baseline to Week 52 will be analyzed using a Mixed Model for repeated Measure (MMRM) with treatment, visit, visit-by-treatment interaction, randomization stratification, and baseline total NSAA score. The primary analysis will be based on the ITT population.

As sensitivity analysis, the analysis of covariance model (ANCOVA) model with Multiple Imputations (ANCOVA –MI) will be also applied. There will be 2 sets of multiple imputations performed for the missing data based on the two missing data pattern assumptions separately. One assumption of the missing data pattern is missing at random (MAR). Under the MAR assumption, the missing data after loss to follow-up will be imputed as continuing the trend of previously observed data, and this will be done separately for each treatment. The other missing pattern is missing not at random (MNAR). Under the MNAR assumption, the missing data after loss to follow-up for the pamrevlumab subjects will be imputed as having the same data distribution as those in the placebo group, and the missing data of the placebo subjects will be imputed as continuing the trend of previously observed data.

After a multiple imputation, the primary endpoint of change in the total score of NSAA will be calculated from the observed and imputed data and will be analyzed using analysis of covariance model (ANCOVA). The ANCOVA model will include the same covariates as in the primary analysis.

The model will include treatment, randomization stratification, and baseline total score of NSAA as covariates. The analysis will be based on the ITT population.

For other secondary endpoints, as appropriate, Mixed Model for Repeated Measure (MMRM) / ANCOVA model will be used in continuous variables; logistic regression model in binary variables; Cox regression model in time-to-event variables. The analysis models will include appropriate baseline factors. Impact of missing data will be evaluated based on various assumptions.

**Safety Analyses:**

All treatment-emergent adverse events (TEAEs) will be summarized by treatment arm, including: TEAEs Grade ≥3, treatment-emergent serious adverse events (TESAEs), deaths, and TEAEs leading to study or treatment discontinuation. Clinically significant changes from baseline in vital signs, laboratory tests will be summarized.

# 2. INTRODUCTION

## 2.1. Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G1 (IgG) kappa monoclonal antibody that binds to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role, as 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 (Emery1991).

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).

The clinical signs of DMD develop at a young age; first clinical symptoms are usually reported before the age of 5 years (Annexstad 2014, Pane 2013). Female carriers are most often asymptomatic but may demonstrate mild symptoms and are susceptible to cardiomyopathies (Bushby 2003, Yiu 2015)

The principal clinical characteristic of DMD is signs of muscle weakness and wasting. Affected children will have difficulties with jumping, running, climbing stairs or rising from the floor due to progressive limb weakness. By the age of 12, they will lose their independent ambulation and become wheelchair-bound (Annexstad 2014; Tsuda 2018; Zhou 2010). Major clinical signs of DMD patients are respiratory impairment, and cardiac dysfunction, leading to multiple organ disabilities and are ultimately the leading cause of morbidity and mortality in patients with DMD. Respiratory manifestations include respiratory muscle weakness, obstructive sleep apnoea, mucus plugging and respiratory failure (Birnkrant 2018). 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).

Dystrophin deficiency in the heart causes cardiomyopathies which are later responsible for cardiac complications. With the progression of the disease, the myocardium fails to meet physiological demands and clinical manifestations of heart failure occur such as fatigue, weight loss, vomiting, abdominal pain, sleep disturbance and inability to operate daily activities (Birnkrant 2018). 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).

Boys treated for DMD have low-trauma extremity fractures as a result of osteoporosis, and 30% may develop symptomatic vertebral and leg fractures due to bone fragility. Osteoporosis is a side effect of glucocorticoid therapy. Those bone manifestations can lead to chronic back pain, spine deformity, bone fractures, scoliosis and premature or permanent loss of ambulation (Birnkrant 2018). As dystrophin is also expressed in the central nervous system (CNS), other clinical manifestations of DMD patients are neuropsychological problems, and neurobehavioral abnormalities (Annexstad 2014; Tsuda 2018; Zhou 2010). Endocrine disturbances also occur in part of adolescents with DMD. Those hormonal disorders provoke a delay in the age of puberty and short stature problems (Annexstad 2014; Leung 2011; Zhou 2010).

Maximal life-expectancy of DMD patients is currently estimated at 30–40 years of age (Walter 2017). Corticosteroid treatment and higher standards of medical care such as artificial respirators have considerably improved survival within the last two decades (Birnkrant 2018; Bushby 2010; Falzarano 2015; van Westering 2015; Wu 2014).

### 2.3. Connective Tissue Growth Factor

Connective tissue growth factor is a 38 kDa secreted matricellular glycoprotein of the cysteine-rich 61/CTGF/nephroblastoma overexpression (aka cellular communication network [CCN]) family (Perbal 2004; Rachfal 2005). It is produced by many cells, including fibroblasts, myofibroblasts, endothelial cells, mesangial cells, and stellate cells. The name “connective tissue growth factor” implies a mechanism of action similar to that of classic growth factors, which signal through specific cell-surface receptors. However, experimental evidence indicates that CTGF, and the other members of the CCN family, have activities associated with matricellular proteins that function in a more subtle modulatory fashion. Matricellular proteins are a subclass of ECM proteins that modulate cellular functions and signaling pathways through multiple mechanisms that depend on cell type and the cellular context. Prototypical representatives of this subclass include secreted protein acidic and rich in cysteine (SPARC), osteopontin, and thrombospondins (Bornstein 2002). Connective tissue growth factor fits squarely within this group of proteins, is generally expressed at high levels during development and in response to injury, and typically binds to multiple cell-surface receptors, ECM components, growth factors, and cytokines (Chen 2009). The cellular functions that can be modulated by CTGF include secretion and/or organization of ECM, cell proliferation, survival, adhesion, migration, and epithelial mesenchymal transformation (EMT). Modulation of cellular signaling appears to occur through interactions of CTGF with 1) cell surface components such as integrins or the low density lipoprotein receptor-related protein (LRP)-1 (a multifunctional endocytic and signaling receptor), 2) cytokines and cytokine inhibitors, and 3) matrix components such as heparan sulfate proteoglycans (HSPGs) and fibronectin. Interactions with HSPGs may displace other HSPG-

binding proteins such as VEGF and bone morphogenetic proteins (BMPs). Binding of cytokines to CTGF may either sequester them in an inactive conformation, or help to present cytokine binding partners to their receptors.

### 2.4. Connective Tissue Growth Factor in Duchenne Muscular Dystrophy

Connective tissue growth factor is a nonstructural regulatory protein present in the ECM that has an important role in fibrosis. Skeletal muscle from DMD patients, dystrophic dogs, and *mdx* mice all show elevated levels of CTGF (Porter 2003; Sun 2008).

Connective tissue growth factor can reproduce or amplify the effects of TGF-ß on fibrosis by inducing collagen type 1, α5 integrin, and fibronectin much more potently than TGF-ß 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 into the medium, and respond to the CTGF by increasing the ECM constituents, partially inhibiting myoblast differentiation and inducing myoblast dedifferentiation (Vial 2008).

In DMD, the role of CTGF might extend well beyond replacement fibrosis secondary to loss of muscle fibers, since its transient overexpression upon adenovirus injection into skeletal muscle induced a transient dystrophic-like phenotype (Morales 2011) and antibody inhibition of CTGF enabled better engraftment of satellite cells (Morales 2013).

A major manifestation of DMD is cardiac fibrosis. Cardiac fibrosis is associated with increased CTGF expression in the *mdx* mouse heart. Connective tissue growth factor may be a key mediator of early and persistent fibrosis in dystrophic cardiomyopathy (Au 2011).

Connective tissue growth factor is critically involved in several chronic fibro degenerative diseases. Pamrevlumab treatment has been shown to positively affect the course of several of these diseases in Phase 1 and Phase 2 clinical studies.

Together, these observations suggest that CTGF may play an important role in DMD and thus, inhibition of CTGF function by pamrevlumab could result in decreased fibrosis in the muscles and possibly increased muscle function.

### 2.5. Clinical Trial Experience with Pamrevlumab

The clinical trial experience with pamrevlumab includes 11 clinical studies across a number of indications, including DMD that are presented in the current Investigator's Brochure.

Overall, pamrevlumab has been well tolerated. The duration of exposure by indication is displayed in the current Investigator's Brochure.

Adverse events (AEs) have been generally mild or moderate in severity and transient in duration. The AEs have been typical of the subjects' underlying medical condition(s). Infusions of pamrevlumab have been well tolerated. There is no apparent pattern to the serious adverse events (SAEs) observed during these clinical trials.

Refer to the Investigator's Brochure for additional information.

## 2.6. Rationale and Risk/Benefit for Pamrevlumab in Duchenne Muscular Dystrophy

The rationale and positive risk/benefit ratio for the 093 study originates in the literature and preliminary safety and efficacy data of the 079 main study, now complete. Please refer to the current Investigator's Brochure for detailed information.

### 2.6.1. Summary of Pamrevlumab Clinical Studies in DMD

| Study Number | Study Title or Description | Country | N<br>Status | Target age of population |
|---|---|---|---|---|
| **Duchenne Muscular Dystrophy** | | | | |
| FGCL-3019-079 | A Phase 2, Open-Label- Study to Evaluate the Safety, Tolerability, and Efficacy of pamrevlumab in Non-Ambulatory Subjects with DMD | USA | 21<br>Main study: (Complete)<br>OLE: (Ongoing) | 12 years and older |
| FGCL-3019-093 | A Phase 3, Randomized, Double-Blind, Trial of Pamrevlumab (FG-3019) or Placebo in Combination with Systemic Corticosteroids in Subjects with Non-ambulatory Duchenne Muscular Dystrophy (DMD) | Global | 90<br>Ongoing | 12 years and older |
| FGCL-3019-094 | A Phase 3, Randomized, Double-Blind, Trial of Pamrevlumab (FG-3019) or Placebo in Combination with Systemic Corticosteroids in Subjects with ambulatory Duchenne Muscular Dystrophy (DMD) | Global | 70<br>Ongoing | 6 < 12 years of age |

### 2.6.2. Rationale for Efficacy Assessments

#### 2.6.2.1. Pulmonary Assessments:

##### 2.6.2.1.1. Forced Vital Capacity (FVC):

Pulmonary dysfunction in DMD is progressive and restrictive in nature and is one of the most common causes of morbidity and mortality in non-ambulatory patients. Forced vital capacity (FVC) assessed by spirometry, is the best global assessment of all respiratory muscles, because it requires a full inspiration (reflecting function of inspiratory muscles) and a full expiration

(reflecting function of expiratory muscles) (Finder, 2017). Pulmonary function tests have an excellent feasibility (defined as the percent of subjects able to perform the task) of > 95% in non-ambulatory DMD patients (Connolly, 2015). With the widespread use of corticosteroids, a delay in pulmonary function decline by 2-3 years has been observed. However, once patients are in the decline phase, a similar rate of decline has been observed regardless of glucocorticoid treatment. Several studies have shown that rates of decline are similar for both steroid- and non-steroid treated patients with DMD once in the decline phase (Mayer, 2015); (Connolly, 2015); (McDonald, 2018a).

Natural history data show that non-steroid and steroid users aged 10 to 18 years had similar changes (decline) in FVC% of 5% to 6% per year (Ricotti, 2019), (Finder, 2017), (Mayer, 2015).

#### 2.6.2.1.2. Forced Expiratory Volume at 1 Second (FEV1):

FEV1 assesses airway function and is the standard global assessment in both clinical and research studies of asthma, chronic obstructive pulmonary disease, and cystic fibrosis. FEV1 is understood to correlate closely with FVC, with the advantage of requiring less prolonged effort (1 second). (Finder, 2017). Data from the placebo group, in the DELOS study (Buyse, 2015) have shown that yearly rates of ppFEV1 decline were -10.2% [SD 2.0] (Meier, 2017).

#### 2.6.2.1.3. Peak Expiratory Flow Rate (PEFR):

Expiratory flows are easily measured and predominantly reflect expiratory muscle function. Full inspiration is needed to achieve maximal flow; therefore Peak Expiratory Flow Rate (PEFR) requires both inspiratory and expiratory muscle function (Finder, 2017). The annual rate of change for ppPEFR was −5.8 ± 0.6%/year (mean ± SE) based on prospective data in DMD patients, collected in the Neuromuscular Clinic at The Children's Hospital of Philadelphia (Philadelphia, PA) from 2005–2010 (Mayer, 2015). In a more recent publication, the 1-year change in ppPEFR was -4.8% (Ricotti, 2019) with N=29.

### 2.6.2.2. Muscle Function

See section 6.2.6.

#### 2.6.2.2.1. Fibrosis and FAT assessment of the Upper Arm (Biceps brachii) assessed by MRI:

In the recent years, several longitudinal studies have reported the potential value of MRI as a biomarker to assess disease progression and treatment effect in DMD. MRI biomarkers provide the advantage of studying different muscle groups in both lower and upper limbs, enabling assessment of disease progression in not only ambulant, but also non-ambulant patients incapable of performing physical tests, in addition to being an objective measure not influenced by patient's motivation during functional tests (Szigyarto, 2018).

T2-mapping can help determine the level of inflammation, edema and fat infiltration present in the affected muscle (Magrath, 2018).

Overall the preliminary results from the ongoing phase 2 study in non-ambulatory DMD subjects show that pamrevlumab may have a beneficial effect on several clinically meaningful parameters affecting the DMD population. Pamrevlumab, as an antifibrotic agent, has shown the potential to slow disease progression in patients with DMD. That, in addition to being well tolerated in pediatric patients is considered of significant clinical benefit. Therefore, the risk-benefit ratio

remain favorable. For more information please reference the current Investigator's Brochure. Additionally, to date there has been no important identified risk to this study population (age 6 to <12) vs the non-ambulatory population, aged 12 years and above.

### 2.6.3. Dose Rationale

The nonclinical safety of pamrevlumab has been evaluated in three juvenile toxicity studies in Sprague Dawley rats. FibroGen has conducted a 2-week non-GLP and a 1-month GLP study initiated in postnatal day (PND) 21 rats and a non-GLP 2-week tolerability study initiated in PND 7 rats.

To date pamrevlumab has been well tolerated at all doses tested in all nonclinical safety studies conducted with no pamrevlumab-related target organ toxicities observed in the GLP repeated dose toxicity studies in adult animals to support general development of pamrevlumab or in the GLP toxicity study conducted in juvenile rats (PND 21) in support of the pediatric indication. There was a pamrevlumab-related increase in prostate weights in PND 21 rats at the high dose (100 mg/kg) in the 2-week dose range finding (DRF) study (FibroGen Study No. 352015011) at a rat/human exposure ratio (AUC) of 2.2 compared to the DMD clinical study (Study FGCL-3019-079). The No Observed Adverse Effect Level (NOAEL) in this 2-week DRF study was 30 mg/kg with an exposure ratio (AUC) of 0.6 (Table 1). However, this prostate effect was not reproduced at the NOAEL of 200 loading dose/100 mg/kg maintenance doses in the subsequent GLP 4-week study (352016001). In this 4-week study, PND 21 rats received 9 doses of pamrevlumab over 4 weeks as opposed to 4 administrations of pamrevlumab over 2 weeks in the DRF study resulting in similar exposure (AUC) ratio of 2.2 at the NOAEL (Table 1). In addition, pamrevlumab was well tolerated in a 2-week tolerability study when administered to PND 7 rats at doses of 50 and 200 mg/kg TIW for 4 weeks resulting in an exposure ratio at the NOAEL (200 mg/kg) of 4.6, with a trend of decreased body weight and body weight gain at 50 and 200 mg/kg (Table 1). However, these body weight effects were not considered adverse, as they were not dose related and appeared to rebound during the recovery period.

**Table 1. Pamrevlumab plasma exposures in male rats and DMD patients**

| Study Type (Study Number) | High Dose (mg/kg) and Regimen | Cmax (µg/mL) | AUC (hr*µg/mL) | Cmax ratio (Rat/Human) | AUC ratio[a] (Rat/human) |
|---|---|---|---|---|---|
| 2-week Juvenile Rat DRF (352015011) | 30 (NOAEL) | 523 | 32000 | 0.5 | 0.6 |
| | 100 2X/week | 1805 | 118000 | 1.9 | 2.2 |
| 1-month Juvenile Rat GLP (352016001) | 200/100 2X/week (NOAEL) | 1805[b] | 118000[b] | 1.9[b] | 2.2[b] |

| | | | | | |
|---|---|---|---|---|---|
| 2-week Juvenile Rat Tolerability DRF (352020009) | 200 3Xweek (NOAEL) | 4660 | 163000 | 4.8 | 4.6 |
| DMD Clinical Study (FGCL-3019-079) | 35 Once every two weeks | 970 | 212000 | NA | NA |

[a]AUC ratios include a "correction factor" of 6 (Q2W in clinic vs three-times-weekly in rats) or 4 (Q2W in clinic vs. three times weekly in rats)

[b]estimated conservatively based on 2-week Juvenile Rat DRF study (352015011). Full TK was not conducted in this study; presence of pamrevluamb was evaluated in plasma samples collected on PND 50, 24 hours after the final dose and on PND 77 after recovery.

Together, the totality of the nonclinical safety data for pamrevlumab in juvenile rats suggest the 35 mg/kg dose of pamrevlumab administered every 2 weeks proposed for the non-ambulatory patients old DMD patients >12 years would be well tolerated in patients < 12 years of age.

To date, there is no clinical data available for subjects who are 6-<12 years old. FibroGen is planning to share all available clinical data upon completion of study 094 for ambulatory DMD subjects, in the future.

### 2.6.3.1. Pharmacokinetics

The PK parameters of pamrevlumab have been evaluated in subjects with idiopathic pulmonary fibrosis (studies FGCL-MC3019-002 and FGCL-3019-049), subjects with pancreatic cancer (Study FGCL-MC3019-028), and subjects with diabetic nephropathy (Study FGCL-3019-MC003). PK data in DMD subjects are available from the ongoing study 079. Study results are summarized below.

### 2.6.3.2. Single-Dose Idiopathic Pulmonary Fibrosis Study FGCL-MC3019-002

Pharmacokinetics parameters of pamrevlumab were evaluated in 21 subjects receiving single dose intravenous infusions of 1, 3, and 10 mg/kg pamrevlumab over at least 120 minutes. Cmax (µg/ml) values were: 24.58, 123.7 and 274.8 for the three doses respectively. Tmax was 2 hours in all groups. AUC (µg.h/ml) values were: 2181, 13280 and 33190 respectively for the three doses.

Globally, the AUC and Cmax increased with the dose over the studied dose range. The plasma elimination rate for pamrevlumab slowed with dose increase, suggesting that a saturable process may be involved in pamrevlumab elimination. Both one-compartment and two-compartment PK models adequately described the elimination phase after a single pamrevlumab infusion. The 3 mg/kg cohort exhibited a lower effective volume of distribution as a percentage of body weight, leading to a higher Cmax than would be expected on the basis of normalized dose. This difference in the 3 mg/kg cohort may be due to the increased mean body mass index in this group (approximately 34 kg/m$^2$, compared to 29 kg/m$^2$ in other cohorts).

#### 2.6.3.3. Single and Multiple-dose PK in Subjects with Incipient Nephropathy Due to Type 1 or Type 2 Diabetes Mellitus (FGCL-3019-MC003)

**Single dose:** The PK of pamrevlumab after administration of single doses of 3 and 10 mg/kg was evaluated in 23 subjects with incipient nephropathy due to type 1 or type 2 diabetes mellitus (PK report Study FGCL-MC3019-003). In general, the AUC and Cmax increased more-than-proportionally to dose over the dose range in this study. Mean t½ was 73 and 141 hr at 3 and 10 mg/kg respectively. Considering the variability among the individuals and between studies, the clearance and volume of distribution values appeared to be comparable between the different subject populations at comparable pamrevlumab doses.

**Multiple dose**: The PK of pamrevlumab after administration of multiple IV doses of 3 and 10 mg/kg was evaluated in 18 subjects with incipient nephropathy due to type 1 or type 2 diabetes mellitus (PK report Study FGCL-MC3019-003). Cmax at Day 0 was 72.9 ± 20.9 in the group receiving 3 mg/kg and 420 ± 211 in the group receiving 10 mg/kg. Tmax(h) at day 0 was: 2.25 in the 3mg/kg group and 3.04 in the 10mg/kg group. Mean t½ at day 0 was 73.3±16.8 and 141±25.3 at 3 and 10 mg/kg respectively. At day 42, Cmax values were: 76.0 ± 11.1 in the 3 mg/kg group and 511 ± 310 in the 10 mg/kg group. Tmax values recorded at day 42 were respectively 4.12 and 6 in the two doses groups. In general, the AUC and Cmax also increased more-than-proportionally to dose over the studied dose range. Mean t½ at day 42 was 102 and 135 hr at 3 and 10 mg/kg respectively, indicating the same trend of increasing t½ with this comparable dose range that was observed in other studies. There was a decrease in systemic clearance values between Day 0 versus Day 42 and an increase in exposure following repeated dosing compared to the exposure after single (first) dose, which is expected based on the t½ and the Q2W dosing interval. A comparison of trough levels (Day 42 versus Day 56) suggested that steady state had been reached before Day 42, which is consistent with the t½ values.

#### 2.6.3.4. Multiple-Dose Idiopathic Pulmonary Fibrosis Study FGCL-3019-049

Plasma PK of pamrevlumab after administration of multiple doses of 15 and 30 mg/kg every 3 weeks (Q3W) was evaluated as an exploratory endpoint in Study FGCL-3019-049 which enrolled 89 subjects with idiopathic pulmonary fibrosis. Cmax (µg/ml) mean values reported after the 1st, 9th, and 16th doses were respectively 332±85, 349±106 and 324±134 at the 15 mg/kg dose. Cmax (µg/ml) mean values reported after the 1st, 9th, and 16th doses were respectively 815±219, 860±207 and 804±165 at the 30 mg/kg dose. Cmin (µg/ml) mean values after the 1st, 9th, and 16th doses were respectively 21±9, 39±24 and 44±24 at the 15 mg/kg dose. Cmin mean values after the 1st, 9th, and 16th doses were respectively 99±44, 217±115 and 174±80 at the 30 mg/kg dose.

Overall, Cmax and Cmin values were consistent with those at similar time points of comparable doses in previous studies. Cmax and Cmin increased with increasing dose from 15 mg/kg to 30 mg/kg.

There was a general trend of increasing Cmax and Cmin with repeated dosing from first dose to 9th or 16th dose, which is consistent with the t½ of pamrevlumab and dosing regimen of once Q3W. With a plasma t½ of approximately 1 week (determined from previous studies), the steady state was expected be reached after several doses (i.e., by the 9th dose). This is generally consistent with the observed PK data in this study. For example, the comparable mean/median Cmin and Cmax values at 9th and 16th doses for Cohort 2 (30 mg/kg) were slightly higher than those at Day 1. For Cohort 1 (15 mg/kg), the mean/median Cmax values at 16th dose time point

was slightly lower than those on 1st and 9th dose. However, the decrease was probably due to a reduction in the number of subjects at 16th dose time point and an increase in Cmax variability, rather than an actual decrease in exposure over repeated dosing (from 9th to 16th dose).

PK sampling was conducted at only 2 time points (post-dose and pre-dose) between doses, so t½ estimates were not available from this study.

#### 2.6.3.5. Multiple-Dose Pancreatic Cancer Study FGCL-MC3019-028

In Study FGCL-MC3019-028, 75 subjects with pancreatic cancer were enrolled. Pamrevlumab was administered in combination with gemcitabine/erlotinib. Plasma PK of pamrevlumab was evaluated as a secondary endpoint after administration of multiple doses. Six cohorts were dosed at 3, 10, 15, 25, 35, or 45 mg/kg Q2W, and 2 cohorts dosed weekly at either 35 mg/kg on Day 1 followed by 17.5 mg/kg weekly or 45 mg/kg on Day 1 followed by 22.5 mg/kg weekly.

Based on the available pamrevlumab plasma-concentration data:

- $C_{min}$ and $C_{max}$ values increased with increasing dose. Analysis of $C_{max}$ indicated that increases were dose proportional.
- $C_{min}$ and $C_{max}$ values generally increased with repeated dosing, which is consistent with the dosing regimens and $t_{½}$ of pamrevlumab.
- Pamrevlumab exposure (based on estimated AUC values) generally increased with increasing dose.
- Overall, $C_{min}$ and $C_{max}$ values were comparable to those at similar doses in previous studies.
- On Day 1, $T_{max}$ was 3 hours from the start of dosing and 1 hour from the end of the infusion. On Day 43, $T_{max}$ was 2 hours from the start of dosing and 1 hour from the end of the infusion.
- After the first dose, the estimated median $t_{½}$ increased from 2.4 days for the 3 mg/kg dose to 4.5-8 days for doses ≥10 mg/kg. After repeated dosing (on Day 43), the estimated median $t_{1/2}$ increased from 2.6 days for the 3 mg/kg dose to 6.6–9.0 days for doses ≥10 mg/kg.
- Estimated $t_{½}$ values for doses >10 mg/kg did not appear to increase markedly with dose, based on available data (limited time points) averaging to approximately 1 week, (the highest 2 dose regimens [35 and 45 mg/kg every two weeks] showed a median value of 7.85 and 7.29 days, respectively).

#### 2.6.3.6. Single/multiple Dose PK in DMD subjects in Study FGCL-3019-079

Pharmacokinetic sampling was conducted in study FGCL-3019-079, where DMD subjects were dosed with 35 mg/kg pamrevlumab once every 2 weeks. PK samples were collected at predose, <1h after end of infusion, and on Days 2, 4, 7, 10 and 14 following the first dose, as well as at steady-state at weeks 26 and 52 (predose at both times, and post dose at week 52). Pamrevlumab concentrations were measured in all plasma samples. After preliminary PK analysis (NCA) based on preliminary concentration-time profiles of each individual, the PK parameters from this study (Table 2) appeared to be comparable to those obtained from previous PK studies (study FGCL-MC3019-002 and study FGCL-3019-MC003; respectively), suggesting that the pamrevlumab exposures in pediatric DMD subjects were comparable to those in adults, without

any marked exposure/PK difference between various disease of patient populations, which were shown in dose-justification analysis by population PK/PD exploration.

**Table 2: PK parameters in study FGCL-3019-079 following a single dose**

| | $T_{max}$ (hr) | $C_{max}$ (μg/mL) | $AUC_t$ (hr*μg/mL) | $AUC_{0-\infty}$ (hr*μg/mL) | $t_{1/2}$ (day) | CL (mL/hr/kg) | $V_z$ (mL/kg) | $V_{ss}$ (mL/kg) |
|---|---|---|---|---|---|---|---|---|
| **Mean** | **2.73** | **970** | **145000** | **212000** | **8.77** | **0.174** | **52.1** | **50.6** |
| **SD** | **0.756** | **307** | **34000** | **49200** | **1.83** | **0.0427** | **15.2** | **14.7** |
| **Median** | **2.68** | **904** | **144000** | **215000** | **8.76** | **0.163** | **50.2** | **48.0** |

### 2.6.4. Safety Summary

Overall, pamrevlumab appears to be well-tolerated. As of the data cutoff date, 1723 subjects have received study drug (pamrevlumab or placebo) in the pamrevlumab clinical program including both completed and ongoing studies (1036 subjects in studies that are blinded at the time of this IB) comprising 420 subjects with pancreatic cancer, 829 subjects with IPF, 112 subjects with liver fibrosis secondary to hepatitis B, 20 subjects with COVID-19, 190 pediatric subjects with DMD, 107 subjects with diabetic neuropathy (DN), 2 pediatric subjects with focal segmental glomerulosclerosis (FSGS), and 43 healthy subjects. For additional information on the safety of pamrevlumab in the completed DMD study (079) and other indications, please refer to the current version of the Investigator's Brochure.

# 3. OBJECTIVES AND ENDPOINTS

## 3.1. Objective

To evaluate the efficacy and safety of pamrevlumab versus placebo in combination with systemic corticosteroids administered every two weeks in ambulatory subjects with Duchenne muscular dystrophy (age 6 to <12 years).

## 3.2. Endpoints

### 3.2.1. Primary Endpoint

Ambulatory functional assessment:

- Change in North Star Ambulatory Assessment (NSAA) total score from baseline to Week 52.

### 3.2.2. Secondary Endpoint

Other functional assessments:

- Change in 4-stair climb Velocity (4SCV) assessment from baseline to Week 52.
- Change in the 10-meter walk/run test from baseline to Week 52.
- Changes in Time to Stand (TTSTAND) from baseline to Week 52.
- Time to Loss of Ambulation (LoA) from baseline to Week 52

### 3.2.3. Safety Assessments

- All treatment emergent adverse events (TEAEs), serious adverse events (SAEs), clinically significant laboratory test abnormalities, discontinuation of treatment due to treatment-related AEs and hypersensitivity/anaphylactic reactions.
- Number and percentage of subjects with hospitalizations due to any serious adverse events with pulmonary and/or cardiac cause(s).
- Number and percentage of subjects with bone fractures.
- Annualized height velocity, HV (cm/year) from Baseline to Week 52

### 3.2.4. Exploratory Endpoint

- Change in Duchenne Video Assessment severity percentage from baseline to Week 52.
- Change in ppFVC and ppPEF assessed by spirometry, from baseline to Week 52,

MRI Muscle assessment:

- Changes in lower extremities vastus lateralis muscle fibrosis score from baseline to Week 52, assessed by MRI

### 3.2.5. Pharmacokinetics/pharmacodynamics (PK/PD) assessment

- Population PK/PD analysis.

### 3.3. Overall Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled multi-center trial to evaluate the efficacy and safety of pamrevlumab in ambulatory subjects with DMD over a 52 week period.

Subjects must be fully informed of the potential benefits of approved products and make an informed decision when participating in a clinical trial in which they could be randomized to placebo.

Approximately 70 subjects will be enrolled in this trial, globally. Subjects will be randomized in a 1:1 ratio to one of the two study treatment arms; pamrevlumab or placebo. Randomization will be stratified by exon 44 deletion.

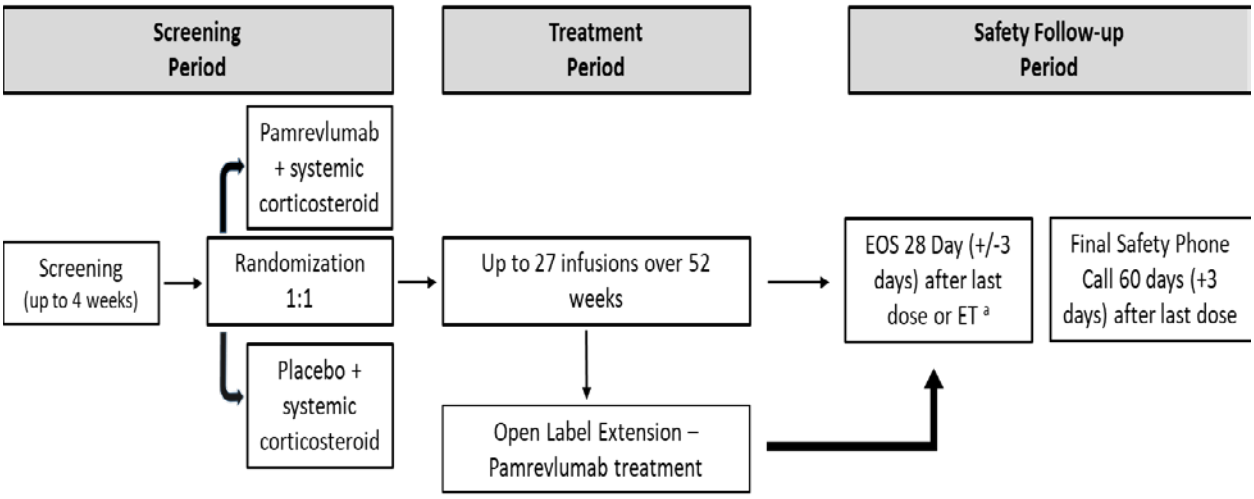
The main study has three study periods:

- Screening period: Up to 4 weeks
- Treatment period: 52 weeks
- Safety Follow-up period/final assessment: A visit 28 days (+/- 3 Days) and a final safety follow-up phone call 60 days (+ 3 Days) after the last dose

Each subject will receive pamrevlumab or placebo at 35 mg/kg every 2 weeks for up to 52 weeks. Subjects who complete 52 weeks of treatment may be eligible for an open-label extension (OLE), offering extended treatment with pamrevlumab.

Subjects who discontinue study treatment for any reason should be encouraged to return to the investigative site to complete final safety and efficacy assessments.

**Figure 1 Study Scheme**




Abbreviations: EOS= End of Study, ET=Early Termination
a) Subjects who discontinue the study early, for any reason, will complete an early termination visit 28 days (+/- 3 Days) and a final safety follow-up phone call 60 days (+ 3 days) after the last infusion.

#### 3.3.1. Study Duration

All subjects are encouraged to complete up to 27 doses of study treatment, an End of Study (EOS)/Safety follow-up visit 28 days (+/- 3 Days) and a final safety follow-up phone call 60

days (+ 3 Days) after the last dose. Subjects, who discontinue the study early, for any reason, will need to come in for an early termination visit (ET) 28 days (+/- 3 Days) and a final safety follow-up phone call 60 days (+ 3 Days) after the last infusion. If a patient withdraws from the study after randomization and prior to dosing, an ET visit and safety follow-up phone call are not required. See also Section 4.3 for mandatory discontinuation reasons, and for procedures related to the ET.

Subjects who complete the study may be eligible for rollover into an open-label, extension, which will provide data on the long-term safety and efficacy of pamrevlumab.

End of trial is defined as the date at which the last subject completes the final safety follow-up phone call.

### 3.3.2. Placebo Control Group

In order to evaluate the effect of treatment with pamrevlumab approximately 50% of subjects will be randomized to placebo treatment.

For DMD subjects one of the only treatment options is systemic corticosteroids. Therefore, placebo control, given with systemic corticosteroids, is appropriate and ethical. All study subjects who are eligible, including those randomized to placebo and who complete the study, will be given the option to crossover to the active arm in the open label extension, which will provide data on the long-term safety and efficacy of pamrevlumab.

## 3.4. Subject ID, Randomization and Treatment Assignment

### 3.4.1. Subject ID

All subjects will be assigned an 8 digit subject ID number consisting of a four digit site number and a 4 digit subject ID starting with [redacted]. Subject numbering will be assigned sequentially per site as subjects are recruited/screened (e.g., [redacted], [redacted], and [redacted], etc.). The first subject enrolled at each site will have a subject ID of [redacted].

### 3.4.2. Randomization

Approximately 70 subjects will be randomized 1:1 to receive either pamrevlumab or placebo, resulting in approximately 35 subjects in treatment arm A and 35 subjects in treatment arm B. Each subject will receive a unique 3 digit randomization code.

Randomization schedules will be prospectively prepared. Automated randomization and treatment assignments will be performed by an Interactive Response System (IXRS or IRT).

**Randomization will be stratified by exon 44 deletion (Yes/No) for analysis. Stratification has no impact upon treatment assignment nor dosage.**

### 3.4.3. Treatment Assignment

Subjects will be randomized 1:1 to one of two treatment arms:

| Arm A | Arm B |
|---|---|
| pamrevlumab 35 mg/kg IV Q2 weeks + systemic deflazacort or equivalent potency of corticosteroids administered orally | matching placebo IV Q2 weeks + systemic deflazacort or equivalent potency of corticosteroids administered orally |

## 3.5. Blinding

This is a double-blind, placebo-controlled study. The Investigator, study site staff, subjects, selected sponsor clinical team and designees are blinded to study drug assignment. Blinded treatment with a placebo control is the gold standard method for obtaining unbiased assessments of safety and efficacy in clinical trials of investigational drugs such as pamrevlumab.

### 3.5.1. Maintenance of Blinding

The study blind will be maintained for all parties specified above throughout the study. Pamrevlumab and placebo will be identical in appearance, packaging, and labeling in order to maintain the study blind. The blind will remain intact even while subject rollover into the open label extension and until the database is locked for the main study.

### 3.5.2. Request for Unblinding of Treatment Assignment

Investigators, study site staff and subjects will remain blinded to treatment assignments until study completion and database lock.

Breaking the blind during the study (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the Investigator due to immediate safety concerns, or is considered essential for the immediate subject management. FibroGen approval is not a prerequisite for the investigator to unblind a subject. It is the responsibility of the investigator to promptly document and notify the Sponsor of any unblinding.

The IRT system allows authorized users to break the blind for a specific subject. Detailed instructions for unblinding are provided in the IRT user manual.

# 4. SELECTION AND WITHDRAWAL OF SUBJECTS

## 4.1. Subject Inclusion Criteria

In order to be eligible for inclusion in this trial, a subject must meet all of the following:

**Age, Consent:**

1. Males at least 6 to < 12 years of age, at screening initiation
2. Written consent by patient and/or legal guardian as per regional/ country and/or IRB/IEC requirements

**DMD Diagnosis:**

3. Medical history includes diagnosis of DMD and confirmed Duchenne mutation, including status of exon 44 using a validated genetic test

**Pulmonary criteria:**

4. Average (of Screening and Day 0) percent predicted FVC above 45%
5. On a stable dose of systemic corticosteroids for a minimum of 6 months, with no substantial change in dosage for a minimum of 3 months (except for adjustments for changes in body weight) prior to screening. Corticosteroid dosage should be in compliance with the DMD Care Considerations Working Group recommendations (e.g. prednisone or prednisolone 0.75 mg/kg per day or deflazacort 0.9 mg/kg per day) or stable dose. A reasonable expectation is that dosage and dosing regimen would not change significantly for the duration of the study.

**Performance criteria:**

6. Able to complete 6MWD test with a distance of at least 270 M but no more than 450 M on two occasions within 3 months prior to Randomization with ≤10% variation between these two tests.
7. Able to rise (TTSTAND) from floor in <10 seconds (without aids/orthoses) at screening visit.
8. Able to undergo MRI test for the lower extremities vastus lateralis muscle.

**Vaccination:**

9. Agreement to receive annual influenza vaccinations during the conduct of the study.

**Laboratory criteria:**

10. Adequate renal function: cystatin C ≤1.4 mg/L
11. Adequate hematology and electrolytes parameters:
    a. Platelets >100,000/mcL
    b. Hemoglobin >12 g/dL
    c. Absolute neutrophil count >1500 /µL
    d. Serum calcium (Ca), potassium (K), sodium (Na), magnesium (Mg) and phosphorus (P) levels are within a clinically accepted range for DMD patients.

12. 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

### 4.2. Subject Exclusion Criteria

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

**General criteria:**

1. Concurrent illness other than DMD that can cause muscle weakness and/or impairment of motor function
2. Severe intellectual impairment (eg, severe autism, severe cognitive impairment, severe behavioral disturbances) preventing the ability to perform study assessments in the Investigator's judgment
3. Previous exposure to pamrevlumab
4. BMI ≥40 kg/$m^2$ or weight >117 kg
5. History of:
    a. allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies
    b. hypersensitivity to study drug or any component of study drug
6. Exposure to any investigational drug (for DMD or not), in the 30 days prior to screening initiation or use of approved DMD therapies (e.g., eteplirsen (exondys 51), ataluren, golodirsen (vyondys 53), casimersen (amondys 45)) within 5 half-lives of screening, whichever is longer with the exception of the systemic corticosteroids, including deflazacort

**Pulmonary, Renal, and Cardiac criteria:**

7. Requires ≥16 hours continuous ventilation
8. Poorly controlled asthma or underlying lung disease such as bronchitis, bronchiectasis, emphysema, recurrent pneumonia that in the opinion of the investigator might impact respiratory function
9. Hospitalization due to respiratory failure within the 8 weeks prior to screening
10. Severe uncontrolled heart failure (NYHA Classes III-IV), or renal dysfunction, including any of the following:
    a. Need for intravenous diuretics or inotropic support within 8 weeks prior to screening
    b. Hospitalization for a heart failure exacerbation or arrhythmia within 8 weeks prior to screening
    c. Patients with glomerular filtration rate (GFR) of less than 30 mL/min/1.73m2 or with other evidence of acute kidney injury as determined by investigator
11. Arrhythmia requiring anti-arrhythmic therapy
12. Any other evidence of clinically significant structural or functional heart abnormality

13. **Clinical judgement:** The Investigator judges that the subject will be unable to fully participate in the study and complete it for any reason, including inability to comply with study procedures and treatment, or any other relevant medical, surgical or psychiatric conditions

### 4.3. Subject Withdrawal Criteria and Procedure

Subjects may withdraw from the study at any time, for any reason. If a subject or investigator determines subject should discontinue from treatment, the subject has the option to remain on study. If the subject remains on study, they should continue to perform on-study assessments until the end of study visit or subject terminates for one of the below reasons.

Reasons for withdrawing the subject from the study include the following:

- Any safety concern in the Investigator's opinion, that precludes further study participation
  - Pamrevlumab will be permanently discontinued in case of serious or life-threatening allergic reactions
- Major protocol deviation to inclusion/exclusion that substantially affects subject safety
- Withdrawal of Consent (reason of withdrawal should be obtained)

Subjects who discontinue the study early will complete an Early Termination visit 28 days (+/- 3 days) and complete a final safety follow-up phone call 60 days (+3 Days) after the last infusion. If subject is randomized but not dosed with IP before Early Termination on Day 0, an Early Termination visit is not required.

Note: At the Early Termination visit, MFTs (NSAA, 4-Stair Climb Velocity, 10M Walk/Run, Time to Stand, and Loss of Ambulation (LOA) assessment) should be conducted. MRI does not have to be repeated if the last one was performed within 4 weeks of this visit.

### 4.4. Replacement of Study Subjects

All randomized subjects will be included in the study. Subjects who discontinued the study early will not be replaced.

### 4.5. Study Termination

FibroGen reserves the right to close any investigational site(s) or terminate the study at any time for any reason. Reasons for the closure of the study site or termination of a study by FibroGen may include (but are not limited to):

- Successful completion of the study at the investigational site
- The required number of subjects for the study has been recruited
- Failure of the Investigator to comply with the protocol, GCP guidelines or local requirements
- Safety concerns
- Inadequate recruitment of subjects by the Investigator

# 5. TREATMENT OF SUBJECTS

## 5.1. Study Treatment

### 5.1.1. Pamrevlumab or Placebo

Pamrevlumab is a fully human IgG1 kappa monoclonal antibody that binds to CTGF and is formulated as a solution for administration by IV infusion. Peripheral or central venous access may be utilized at the discretion of the investigator.

Matching placebo is formulated as a solution to be administered in a manner that is identical to pamrevlumab infusion.

### 5.1.2. Formulation

Pamrevlumab is supplied in single-use glass vials containing 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.

The placebo formulation is of identical composition as the pamrevlumab formulation, except for the absence of pamrevlumab.

### 5.1.3. Study Drug Packaging and Labeling

Labels will be prepared and will comply with Good Manufacturing Practice requirements for labelling and local regulatory guidelines.

### 5.1.4. Study Drug Storage

Vials of pamrevlumab and placebo 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. Details regarding the reporting of temperature excursions can be found in the study Investigational Product (IP) Manual.

### 5.1.5. Study Drug Preparation

Pamrevlumab or placebo is infused undiluted after pooling the contents of the calculated number of vials in an empty infusion bag (total volume of fluid must not exceed **410 mL**) according to the Dose Preparation Instructions in the IP Manual.

Pamrevlumab and placebo solutions for infusion must be refrigerated (2˚C to 8˚C) and administered within 48 hours of preparation and within 6 hours if left at room temperature after preparation. Pamrevlumab or placebo infusion solutions are administered by IV infusion (peripheral or central venous access), using an infusion set with a 0.2 µm in-line filter. Gravity infusion or use of an infusion pump are both acceptable methods of infusion as per local institutional standards.

### 5.1.6. Study Drug Administration

Dosing for pamrevlumab (or placebo) will be based on the weight obtained at screening and approximately every 12-weeks after Day 0. The total dose of pamrevlumab (or placebo) is not to exceed 4.1g. Subjects weighing more than 117 kg will receive the maximum allowable dose of 4.1g. The dose should be prepared in a volume of fluid that does not exceed 410 mL. IP will be administered after release from the site's pharmacy (or central pharmacy for sites in the United States utilizing home health care) and infused within 48 hours of preparation as long as it is stored from 2-8C after preparation, otherwise, drug should be infused within 6 hours of preparation if stored at room temperature. Study Drug 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). The dose, route, infusion rate and schedule for the administration of pamrevlumab or placebo is provided in Table 3.

**Table 3: Pamrevlumab (or placebo): Dose, Route, and Administration**

| Agent | Dose | Route | Infusion Rate | Frequency |
|---|---|---|---|---|
| Pamrevlumab (or placebo) | 35 mg/kg | IV | Not to exceed 150 cc/hour* | Every 2 weeks (+/- 3 days) |

**Note**: **DO NOT ADMINISTER STUDY DRUG AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.**
*Gravity infusion or use of an infusion pump are both acceptable methods of infusion as per local institutional standards.

Adjustments may be made to further slow the rate of infusion to less than 150 cc/hour in accordance with the investigator's clinical judgement.

The Investigator or a designee with proper medical training must be either present, or immediately available, during the first Study Drug infusion and observation period (approximately 1 hour after the end of IP infusion) for each subject. If a subject has a significant infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences a significant infusion reaction and continues Study Drug dosing, a physician should be immediately available during all subsequent infusions and observation periods at the site. If the Investigator wishes to use premedication, (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs)) for a subsequent infusion, this should be discussed with the FibroGen Medical Monitor or designee.

Infusions are to be continued until the total volume of the IP infusion has been administered. Subjects will remain at the study site for 1 hour after the end of the IP infusion for clinical observation for all study infusions.

IP will be administered at a hospital or ambulatory setting with adequate facilities for managing medical emergencies. Medications for the treatment of acute reactions, including anaphylaxis, must be available to study site staff for immediate use. Medications for the treatment of acute reactions, including anaphylaxis, will accompany the HHC nurse.

The Sponsor may consider the use of properly trained HHC staff to administer the infusions of study drugs at the subject's home and corresponding study assessments during the conduct of the study (after the completion of three infusions without safety concerns), consistent with institutional regulations and policies (see Section 5.1.7 for details). Medication for the treatment

of acute reactions, including anaphylaxis, will be available at the subject's home for access by the home health care (HHC) nurse.

There is no specific treatment for a pamrevlumab overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

### 5.1.7. Home Health Care (HHC)

HHC may be available to some subjects and will be a decision driven by a combination of the request from the study site, the availability of qualified service in the subject's country, the needs/circumstances of the subject, and Sponsor decision on overall feasibility. Subjects who have previously experienced an infusion reaction will not be allowed to participate in HHC. Medications for the treatment of acute reactions, including anaphylaxis, are required to be available in the patient's home for all IP administration visits. The pharmacy is required to dispense anaphylaxis medication for the first home visit, as the HCP will store it in a lockbox in the patient's home until the end of the study. Following any adverse reaction at an HHC visit, the subject should speak to the study doctor and make a visit, if needed. The subject should also have his next scheduled infusion performed on site until the investigator deems it safe for the subject to return to home infusions. HHC support will only be on weeks where no other assessments besides infusions are being completed. PI maintains overall responsibility for patient careand their participation in the study. The HHC vendor requires PI signature on the PI Oversight Form, which outlines each GCP PI oversight responsibility and the supporting HHC vendor process. The Sponsor maintains oversight of the HHC vendor.

### 5.1.8. Missed Dose

Every attempt should be made to complete all study visits within window.

Visit dates are scheduled based on the previous visits, not the baseline visit. Protocol-defined visits conducted outside the ± 3 day study visit window will be recorded as a protocol deviation. Missed doses are not to be made up through extra visits. If a subject misses more than two infusions in any 8-week period throughout the study, or two sequential infusions, the FibroGen Medical Monitor should be notified. The reason for missed doses must be documented in the subject's clinical record.

Refer to the case report form (CRF) completion guidelines in the Study Reference Manual for additional information on CRF completion requirements for missed visits.

### 5.1.9. IP Handling and Disposal

All IP provided by the Sponsor should be retained at the site until otherwise instructed in writing by the Sponsor (or designee). If local/regional/institutional policies do not allow the site to retain IP, the site must provide the sponsor (or designee) their drug destruction SOP/process for review and approval. The Sponsor (or designee) will perform IP accountability and reconciliation for all IP received at the site prior to approving IP return/destruction. Upon completion of accountability/reconciliation or upon completion of the study or termination of the investigational site, all unused, IP, and all IP that was not dispensed will be shipped to a destruction site designated by the Sponsor (or designee) for destruction. IV bags used to infuse study drug can be disposed of per institutional policy. Please refer to the IP Manual for additional information on study drug materials, management and accountability.

## 5.2. Concomitant Medications

### 5.2.1. Permitted Concomitant Medications

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

Other than the restrictions that follow, concomitant medications may be given at the discretion of the Investigator. It is expected that Investigators will provide optimal medical management of DMD and that subjects may be treated with concomitant medications for their various medical conditions. Optimal medical care must be provided, and Investigators should ensure, for example, that subjects maintain stable vital signs and laboratory test values during the course of the study.

Oral systemic corticosteroids or deflazacort are required, and must be recorded in the clinical chart and the CRF.

There are no safety concerns anticipated with the co-administration of pamrevlumab and COVID-19 vaccine. However, FibroGen recommends a time separation between the administration of a COVID-19 vaccine and blinded study drug (pamrevlumab or placebo) of at least 48 hours to allow for better interpretation of any adverse events and their relationship to the vaccine or study drug. All adverse events should be reported to FibroGen per protocol.

The date of any vaccination administered from the time of screening until the end of the study must be reported in the Concomitant Medications CRF. COVID vaccinations should be captured in the Medical History section of EDC if administered prior to consent. COVID vaccination while on study should be entered into the Concomitant Medication CRF.

### 5.2.2. Prohibited Concomitant Medications

Concomitant medications and therapies that can interfere with a) the course of DMD, b) the protocol endpoint assessments or, c) the study treatments, will not be allowed during the study. Some justified exceptions may apply.

Prohibited medications include any other (approved or investigational) agents for the treatment of DMD. The list of prohibited concomitant medications for treatment of DMD includes, but is not limited to, the following:

- eteplirsen (EXONDYS 51)
- ataluren
- golodirsen (VYONDYS 53)
- Viltolarsen (Viltepso)
- Casimersen (AMONDYS 45)

Questions about concomitant medications should be discussed with the FibroGen Medical Monitor or designee. Patients who are on any approved therapy for DMD should not discontinue the therapy to be eligible for the 094 study. However, if their approved therapy is discontinued for other reasons, they could be considered for participation in this study if they meet all eligibility criteria.

Study drug should not be administered to subjects with a history of allergic or anaphylactic reaction to human, humanized, or chimeric monoclonal antibodies.

### 5.2.3. Contraception Requirements

A non-clinical study evaluating the potential effects of pamrevlumab on embryo-fetal development has been conducted (rabbit embryo-fetal development study 352021017). Preliminary results show the pamrevlumab systemic exposure levels at 200 mg/kg to the pregnant female rabbits which resulted in fetal external and skeletal abnormalities are approximately 20-fold greater than the systemic exposure levels in humans at doses of 30mg/kg or 35 mg/kg in our current protocols.

No adverse effects of pamrevlumab administration were observed in a study of rat male and female fertility.

Recognizing the age range for this study, male subjects who have partners with reproductive potential are required to use contraception (condoms per Clinical Trial Facilitation Group (CTFG) recommendation version 1.1 21-09-2020, Section 2.3) during the conduct of the study and for 12 weeks (3 months) after the last dose of study drug. Permitted contraceptive methods for the subjects include use of a condom (per Clinical Trial Facilitation Group (CTFG) recommendation version 1.1 21-09-2020, Section 2.3) or sexual abstinence during treatment. Sexual abstinence is considered a highly effective method only if definedas refraining from heterosexual intercourse during the entire period of risk associated with IP. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. The package insert regarding reproductive risks associated with the use of corticosteroids used in this study should be evaluated and reviewed with the subject, if applicable.

# 6. ASSESSMENTS OF EFFICACY

## 6.1. Study Assessments

A signed and dated IRB/IEC-approved informed consent must be obtained before any study-specific assessments are performed. Assessments that are part of routine care are not considered study-specific and may be used at screening to determine eligibility. All subjects will be screened for eligibility before randomization. Only eligible subjects will be randomized into the study.

**NOTE**: In accordance with FDA/ EMA Guidance: During the COVID-19 pandemic, the visit modality (e.g.: in-person versus remotely) and scheduling maybe adjusted and conducted at the discretion of the Investigator, in accordance with the site's rules and recommendations, and using all necessary precautions. If a visit has to be done remotely, it can be conducted with any technology available to the site and study subjects, such as via tele-health visits, phone calls, etc.

### 6.1.1. Screening Period

All screening procedures must be performed within 28 days of signing the ICF. Lead times for scheduling MRI may dictate timing of consenting subjects to maintain a 28 day window. Study procedures to be performed during the screening period can be found in the Schedule of Assessments (SOA). Subjects may have a specific procedure such as labs or PFTs repeated during screening to determine if the subject can enter the study. If the subject does not meet eligibility criteria, they must be screen failed. If the investigator feels that the assessments that resulted in screen failure did not adequately represent the subject's eligibility for the study, the subject may be re-screened at the discretion of the investigator. Repeating procedures within the screening window, or screen failing and rescreening a subject should be discussed with the medical monitor to evaluate which procedures should be repeated and when.

Each subject's specific DMD genetic mutation should be entered in the EDC under medical history.

Due to the immunocompromised status of DMD patients, it is recommended the pneumococcal vaccine is administered as per national recommendations and standard of care for Duchenne Muscular Dystrophy patients on corticosteroids prior to study entry.

This vaccination recommendation can be met by administration of any applicable pneumococcal vaccine as per national guidance. This includes both conjugate (PCV13) and polysaccharide (PPSV23) vaccines. Patients should also agree to receive annual influenza vaccinations during the course of the study as needed.

### 6.1.2. Randomized Treatment Period

The Randomized Treatment Phase begins on Day 0 (first infusion of Study Drug) and continues through Week 52. Visit windows are within ± 3 days of the scheduled visit date (14 days from prior visit). Visit dates should be scheduled based on the previous visit, not the baseline visit.

Subjects who complete 52 weeks of treatment may be eligible to rollover into the OLE study where all subjects will be treated with pamrevlumab. If a subject discontinues the main study early for any reason, they will not be eligible for inclusion in the OLE.

### 6.1.3. End of Study/Safety Follow-up

All subjects enrolled will have an EOS/safety follow-up visit 28 days (± 3 Days) and a final safety follow-up phone call at 60 days (+3 days) after the last dose of study treatment. After the protocol-required reporting period (60 days (+ 3 Days) after the last dose), the investigator does not need to actively monitor subjects for SAEs. However, if the investigator becomes aware of an SAE/death that may be possibly related to study treatment after the protocol-required reporting period, the investigator may report the event to FibroGen. SAEs reported outside of the protocol-required reporting period will be captured within the safety database only as clinical trial cases for the purposes of expedited reporting

### 6.1.4. Missed Visits

Visit dates are scheduled based on the previous visits, not the baseline visit. Protocol-defined visits conducted outside the ± 3 day study visit window will be recorded as a protocol deviation. For missed visits, the subject will be asked to resume the planned visit schedule and return for the next scheduled visit.

### 6.1.5. Unscheduled Visits

Unscheduled visits/assessments may be required at the discretion of the investigator. Unscheduled visit data will be captured accordingly in the clinical database.

Subjects who, in the judgment of the PFT or MFT technician or investigator, are unable to perform MFTs ((NSAA, 4-Stair Climb Velocity, 10M Walk/Run, Time to Stand, Loss of Ambulation (LoA assessment)) adequately on a scheduled visit should repeat PFT or MFT assessment as soon as possible, or at minimum ensure to complete PFT or MFTs assessment at the next scheduled visit.

## 6.2. If the subject is unable to perform MFTs at week 52 then the subject must have an unscheduled visit at the nearest possible date to perform MFTs Assessments

Refer to the SOA (Appendix 1) for the main study and Appendix 4 for the OLE study for details regarding the timing and frequency of study assessments. Laboratory evaluations, muscle function tests should be performed prior to infusions.

### 6.2.1. Vital Signs

Vital signs to be collected include; heart rate, blood pressure, respirations and temperature:

- Heart rate should be collected as beats/min
- Respiration rate should be collected as breaths per minute
- Systolic and diastolic blood pressure should be collected from subjects in seated position (mmHg)
- Temperature should be taken as oral or tympanic or using any standard method and captured as °F or °C

#### 6.2.2. Vital signs are collected within 30 minutes before the infusion begins and again within 30 minutes after completion of IP infusion. Physical Exam (including Height and Weight)

A full physical exam is required at screening, throughout the treatment period, and at EOT, EOS or ET.

- Height is collected at Screening, Week 52, preferably by the same trained person. The height measurement should be taken standing against a wall if possible, with a standard height measurement tool (such as a wall-mounted calibrated stadiometer).
- Weight is collected during screening, Week 12, and every 12 weeks (or within 14 days prior) thereafter for dosing adjustment

#### 6.2.3. Laboratory Evaluations

Details regarding sample collection, preparation and transport can be found in the central lab manual.

##### 6.2.3.1. Central Lab Testing

Central lab results obtained during the screening period will be used to determine subject eligibility for participation in the trial.

Central lab results will be reviewed by the investigator for clinical significance and to determine appropriate reporting of adverse events.

**NOTE:** Local laboratory assessments may be used in case of Central Laboratory supply shortages or shipment delays. If local laboratory assessments are used instead of central labs, results will be entered into the clinical database, and the following points need to be considered:

- In case of local screening labs, the Investigator needs to review the results with respect to protocol specified Laboratory Inclusion Criteria for adequate renal function, adequate hematology and electrolytes parameters, and adequate hepatic function.
- For on-study laboratory assessments, only laboratory abnormalities that are considered clinically significant in the Investigator's assessment need to be reported as TEAEs, as per Protocol Section 7.3.7. In such a case, if possible, the etiology of a lab abnormality should be reported as TEAE, not the abnormal lab value.
- For collecting specialty lab samples at a local laboratory:
  - HAHA and HAHA-NA samples should be collected according to the schedule of assessments using local supplies while processing/storing these samples as described in the ICON lab manual.
    - HAHA and HAHA-NA samples may be stored at the clinical site and batch shipped to ICON
    - Other specialty samples (PK) will not be required if local labs are being used

The following labs will be evaluated by a central laboratory:

The maximum total for any blood draw visit is about 1.8 tablespoons 26ml/visit. An additional 1.4 teaspoons (20ml) will be drawn in the event of an immunogenic reaction (see Section 6.2.4.3 for more details)

The total amount of blood drawn throughout the entire study is less than the maximum allowable volume per subject/visit according to recommendations in the article Ethical considerations for clinical trials on medicinal products with minors (September 2017).

Local guidelines and regulations on total blood volume to be drawn within a certain time frame takes precedence over this generalized recommendation.

**NOTE: For example**

- If a subject's weight is **under 30kg**, the additional PK blood draw should not be collected.
- If the subject's weight is **under 20kg**, the additional PK, HAHA, and HAHA-NA blood draws should not be collected.

Glomerular Filtration Rate (GFR) is calculated and resulted by the central lab contracted by the Sponsor for Exclusion Criteria 10c. For subjects 18 years old and under, the "Creatinine – Cystatin C based CKiD equation (Schwartz 2012)" is used. However, it is common for patients with DMD to have very low creatinine to the level where it is below detectable limits and a result cannot be reported. As a result, GFR may or may not be available to support the evaluation of acute kidney injury. Other tests and diagnostic tools for assessment by the investigator should be used in this instance.

| CBC: | Chemistry Panel: |
|---|---|
| Absolute neutrophil count (ANC) | BUN |
| Eosinophils | Creatine Kinase |
| RBCs (Erythrocyte count) | Creatinine |
| Hematocrit % | Chloride |
| Hemoglobin | Magnesium |
| WBCs (Leukocyte count) | ALP |
| Lymphocytes | ALT |
| Monocytes | AST |
| Neutrophils | Bilirubin, total |
| Platelets | Albumin |
| CRP | Phosphorous |
| Basophils | Potassium |
| | Sodium |
| | GGT |
| | Calcium |
| | GFR |
| | Cystatin-C |
| Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = Gamma-glutamyltransferase; BUN = blood urea nitrogen; CBC = complete blood count; RBC = red blood cell; WBCs = white blood cells. CRP= C-reactive protein; GFR = Glomerular filtration rate | |

### 6.2.4. Pharmacokinetics (PK) and Specialty Labs

Additional samples will be collected to evaluate PK and HAHA, HAHA-NA, tryptase in accordance with the SOAs in Appendix 1 and Appendix 2. The central laboratory will manage the storage of these samples while analysis will be performed at a specialty lab(s).

#### 6.2.4.1. Pharmacokinetics

An optional PK assessment will be performed in consenting subjects at timepoints specified in the Schedule of Assessments. For subjects that reconsent to this protocol, PK assessments will continue to be optional except in the case of immunogenic reaction (see Section 6.2.4.3 for more details). Plasma samples will be collected for estimates of PK parameters using population PK and exposure-response analysis, if possible, according to the SOAs in Appendix 1 and Appendix 2. A specialty laboratory will measure plasma pamrevlumab levels using a validated assay. For the population PK analysis, it is critical to accurately record the dosing time and date in addition to the sampling collection time and date. Both pre-dose and post-dose samples are required for PK as specified in Appendix 2. Pre-dose should be within 2 hours prior to the administration of study treatment and post-dose should be between 1-4 hours after administration of study treatment has ended.

#### 6.2.4.2. Human Anti-Human Antibodies (HAHA) and Neutralizing Human Anti-Human Antibodies (HAHA-NA)

Plasma samples will be collected for evaluation of human anti-human antibodies (HAHA), specific to the impact of neutralizing anti-human antibodies (HAHA-NA) and the impact on immunogenicity, in all subjects according to the SOAs in Appendix 1 and Appendix 2. A specialty laboratory will measure HAHA and HAHA-NA titers using validated assays.

Samples/subjects with positive/specific HAHA results will be subject to evaluation of neutralizing antibody (HAHA-NA) assays and analyses. The prevalence and duration of binding and neutralizing antibodies and the effect of these antibodies on the pharmacokinetics, pharmacodynamics markers, efficacy, and safety of pamrevlumab will be assessed.

#### 6.2.4.3. Immunogenic Reactions

Any immunogenic reactions, including drug-related hypersensitivity or anaphylaxis, should have PK, HAHA, HAHA-NA drawn within 24 hours of reaction. (A window of "within 24 hours of reaction" could be at any point following the reaction such as 30 minutes post-reaction but not to exceed 24 hours following reaction). The Tryptase sample should be drawn within 1 to 6 hours of immunogenic reaction, but all samples should at least be collected within 24 hours after the anaphylactic episode. For study visits in which PK, HAHA, and HAHA-NA were drawn as part of the Schedule of Assessments, if an Immunogenic reaction occurs, additional samples still need to be taken within 24 hours of the immunogenic reaction. This will not be considered optional for the subject unless there is local consideration for total blood volume collection on the same day as a standard blood draw timepoint, which could preclude the subject from having this collection take place within 24 hours. See Appendix 2 for more detail.

NOTE: Patients that have an immunogenic reaction that occurs on the same date as a routine study blood draw and weigh less than 30kg, must wait 24 hours prior to drawing the corresponding PK, HAHA, HAHA-NA, and tryptase for immunogenicity per general guidance on the lower limit total blood volume. However, local guidance and regulations should be consulted regarding total blood volume to be drawn within a certain time frame and takes precedence over any general recommendations.

### 6.2.5. Local Pulmonary Function Test (PFT)

A pulmonary function test including FVC, FEV1, and ppPEF, will be collected locally at screening, Day 0, Week 12, Week 22, Week 32, Week 42, and Week 52/EOT. If the test cannot be performed or produces 'Unacceptable' grade results, the PFTs should be repeated during a follow-up visit, or, if an additional visit is not possible the test should be performed at the next scheduled on-site visit. Valid PFT result must be obtained during the Screening Period (within 28days of signing ICF) prior to randomization. Equipment will not be provided by the Sponsor. PFTs should be completed by trained staff.

The inclusion criteria requires that the average percent predicted FVC be above 45%.

### 6.2.6. NorthStar Ambulatory Assessment (NSAA)

The NorthStar Ambulatory Assessment has been developed by the Physiotherapy Assessment and Evaluation Group of the NorthStar Clinical Network. The NorthStar Project is supported by Muscular Dystrophy Campaign. The NorthStar Ambulatory Assessment (NSAA) is a 17-item rating scale that is used to measure functional motor abilities in ambulant children with DMD. It

is usually used to monitor the progression of the disease and treatment effects. Changes from baseline to Week 52 will be measured to assess the primary endpoint.

- Equipment required include a size-appropriate chair or height adjustable plinth, box step, approximately 15 cm high, a mat, a stopwatch, a clear, straight, and marked 10 meters pathway
- The test must be completed without the use of any thoracic brace or leg orthoses. Therapist should ask the subject to complete activities listed in the table below.
- The activities are graded as follows:
  - 2 - "Normal" - no obvious modification of activity
  - 1 - Modified method but achieves goal independent of physical assistance from another
  - 0 - Unable to achieve independently
  - This scale is ordinal with 34 as the maximum score indicating fully-independent function.

### 6.2.7. Other Functional Testing

Subjects will undergo other functional tests including the 6MWD test for eligibility, the 4-stair climb velocity, the 10m walk/run, the time to stand test to evaluate changes from baseline for secondary endpoints. If the test is performed as part of the NSAA assessment, it does not need to be repeated. Appropriate trained and experienced personnel should complete all MFTs. The same evaluator should evaluate the subject at each visit for consistency. All evaluators must be trained and pass proficiency prior to any testing. Video quality control (QC) of the muscle function tests (MFT)will be completed by an external vendor at Screening, Day 0, at Week 52, and additional visits as needed, be evaluated by an independent reviewer to confirm that the evaluator is consistently administering the MFT. Data will be reviewed by independent reviewers on an ongoing basis.

Loss of Ambulation (LoA) can be assessed by the Principal Investigator, Sub-Investigators or Clinical Evaluator (CE), and is defined as an inability to walk without any assisted devices like braces, and/or wheelchairs. Principal Investigator confirms the LoA assessments by signing the LoA eCRFs in EDC.

### 6.2.8. Exploratory Analysis

#### 6.2.8.1. Magnetic Resonance Imaging (MRI)

MRI (Vastus lateralis muscle) assessments will be performed to evaluate fibrosis and to determine any changes in fibrosis score of the lower extremities vastus lateralis muscle fibrosis score, from baseline to Week 52.

- A centralized image interpretation process will provide verifiable and uniform reader training as well as ongoing management of reader performance. This will ensure quality control of the images and their interpretation and decrease variability in image interpretations, leading to a more precise estimate of treatment effect.

- An Independent blinded Centralized Imaging Charter will be formed to interpret the MRIs. Standardization is important for the clinically used MRI measures of vastus lateralis muscle fibrosis and is essential for the imaging secondary endpoint, to reduce variability and to ensure interpretability of the results. The charter will be formed according to the FDA Guidance for Industry: "Clinical Trial Imaging Endpoint Process Standards".

#### 6.2.8.2. Duchenne Video Assessment

The Duchenne Video Assessment (DVA) tool provides a standardized way to document and assess patient quality of movement. Caregivers will follow a standardized script to video record subjects doing specific movement tasks remotely using a secure mobile application within 2 weeks prior to the clinic visits specified in the Schedule of Assessments.

Trained physical therapists will score the videos in a secure scoring dashboard using scorecards with pre-specified compensatory movement criteria. The vendor that developed the DVA, will manage DVA data collection, quality, and scoring.

Caregivers will register for the study mobile application, and they will download the mobile application on an Apple (IOS 10+) or Android (5.1+) smartphone. They will be provided with an eligible smartphone if they do not have access to one. Caregivers will be provided with training materials in the study mobile application and in the study materials provided to each subject to learn how to video record the assigned movement activities. The training materials will describe how to standardize the lighting, clothing, and set-up during the video recording and how to submit videos securely to study staff using the study mobile application. Caregivers will provide an electronic signature within the study mobile application to document training completion.

The specific movement activities are detailed in the Caregiver Manual. Caregivers will be provided with study supplies.

In addition to assigned movement tasks, all subjects will complete one caregiver choice activity and new ability videos (if applicable). The caregiver choice activity is an activity that the caregiver will select prior to Baseline data capture and is an activity they are currently watching when they want to see whether the patient is getting stronger, weaker, or staying stable. The caregiver will video record the same caregiver choice activity throughout the study. If caregivers observe the subject gaining a new ability during the study, they can video record the new ability at any time during the study in the study mobile application.

The DVA vendor study staff will monitor data collection to ensure that each video meets quality standards. If videos need to be re-recorded, caregivers will be contacted about re-recording the video.

**NOTE**: Belgium and China Only: Duchenne Video Assessments will be not be conducted. The DVA vendor services and their mobile application should not be used. There is no alternative for the DVA. All references to DVA or the DVA vendor in the study protocol are not applicable for Belgium and China.

# 7. ASSESSMENT OF SAFETY

## 7.1. Background

Adverse event (AE) reports the critical building blocks to the development of the safety profile of the IP. Subjects should be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 1. In addition, all AEs reported spontaneously during the course of the study will be recorded. The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject as defined in the study protocol are recorded in the subject's medical record and in EDC. The investigator must immediately (within 24 hours of awareness) report to the sponsor or designated safety management vendor all serious adverse events (SAEs), regardless of whether the investigator believes they are related to the study drug.

## 7.2. Definitions

### 7.2.1. Definition of an Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (e.g., diabetes, migraine headaches and gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery, or a medical procedure while on study, is not considered an adverse event.

### 7.2.2. 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,
- 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 primary cause of death would be the adverse event.

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

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

## 7.3. Procedures for Eliciting, Recording, and Reporting Adverse Events

### 7.3.1. Adverse Event Reporting Period

The safety reporting period begins after the subject has signed the informed consent and ends 60 days (+3 days) after the last dose of IP. It is only required that SAEs that occur after signing consent but before first dose be reported prior, while all AEs and SAEs must be reported thereafter. The investigator should notify the Sponsor 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 7.3.5). Pregnancy reporting requirements are outlined in Section 7.3.6.

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

### 7.3.2. Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will actively seek information from each subject at each visit to document any AEs occurring since the previous visit. All AEs will be documented in response to a general question about the subject's well-being and any possible changes from the baseline or previous visit. There will be no directed questioning for any specific AE. This does not deter the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

If a potential AE is reported or observed during review of a Duchenne Video Assessment video after the first infusion of pamrevlumab or placebo, DVA vendor study staff will report the potential AE to the site.

Whenever possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff. The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse

event. The investigator is expected to follow reported adverse events until stabilization or reversibility.

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"

### 7.3.3. Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the most current National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE v. 5.0) 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.

### 7.3.4. Assessing the Adverse Event's Relationship to IP

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 of the 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

### 7.3.5. Reporting Serious Adverse Events (SAEs)

The investigator is responsible for ensuring that all SAEs observed by the investigator or reported by the subject that occur after signing of the informed consent/assent through 60 days (+3 days) after the last dose of pamrevlumab are recorded in the subject's medical record and are submitted to the Sponsor. All SAEs must be submitted to the Sponsor within 24 hours following the investigator's knowledge of the event via the SAE report form. Additionally, pamrevlumab related SAEs (including deaths) that occur after the EOS/safety follow-up visit will be reported.

If a subject is permanently withdrawn from protocol required therapies because of a serious adverse event, this information must be submitted to the Sponsor. The Sponsor will report SAEs and/or suspected unexpected serious adverse reactions (SUSARs) as required to regulatory authorities, investigators/institutions, and central IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

There is no requirement to monitor study subjects for SAEs following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to the Sponsor. In some countries (e.g. European Union [EU] member states), investigators are required to report SAEs that they become aware of after the completion of the study. If SAEs are reported, the investigator is to report them to the Sponsor within 24 hours following the investigator's knowledge of the event. SAEs reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting; these cases will not be included in the clinical study report.

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 EDC. 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).

#### 7.3.5.1. 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.

#### 7.3.5.2. Deaths

The investigator will report the fatal event to the Sponsor's medical monitor. The investigator must provide a causal assessment of the relationship of the event to the study drug.

If the death occurred within the AE collection and reporting period (signed ICF to 60 days (+3 days) after last dose) and meets the reporting criteria, the investigator must submit the SAE Report Form. If the investigator becomes aware of a death occurring after the AE reporting period and considers it related to pamrevlumab, it will be reported as an SAE.

### 7.3.6. Pregnancies: Reporting and Follow-up of Female Partners of Subjects

The outcome of all pregnancies for female partners of male subjects should be followed up and documented as described. If a female partner of a male subject becomes pregnant while the subject is receiving study treatment or within 12 weeks after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to the 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.

Pregnancy itself is not an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Pregnancies are followed up to outcome even if the subject was discontinued from the study. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

### 7.3.7. 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 results provided by the central laboratory throughout the study in a timely manner, and determine whether any abnormal laboratory values are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. 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.).

Clinically significant laboratory abnormalities will be reported as AEs. 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.

### 7.3.8. Hypersensitivity/Anaphylactic Reactions:

Hypersensitivity and anaphylactic reactions will be monitored throughout the study, using the criteria below as defined per Sampson et al. 2006 (Sampson, 2006).

Anaphylaxis is highly likely when the following criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

And at least one of the following criteria:

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient.

### 7.3.9. Safety Monitoring

Safety will be assessed throughout the study. A medically complete baseline profile of each subject will be established through medical history, a complete physical examination including vital signs and laboratory tests. During the course of the study, vital signs and laboratory tests

will be performed at frequent intervals as described in Appendix 1 and Appendix 2. Any medically significant changes from baseline will be monitored throughout the study and appropriate interventions will be taken accordingly. Safety and tolerability will be monitored closely by the Sponsor.

#### 7.3.9.1. Special Reporting Situations

Special Reporting Situations for the IP; pamrevlumab (or placebo) that require safety evaluation include:

- Overdose (any dose greater than 4.1g)
- Suspected abuse/misuse
- Inadvertent or accidental exposure
- Medication error (e.g. incorrect dose administered)
- Drug-drug interactions

Report special situations to the Sponsor's Safety department or delegate within 24 hours of the investigator's knowledge of the event. See Study Reference Manual for detailed reporting instructions.

#### 7.3.9.2. Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) will be utilized and will be composed of external experts. Composition and responsibilities of the DMC will be defined in a separate DMC charter. The DMC responsibilities will include review of the safety data in addition to the routine Sponsor pharmacovigilance activities.

# 8. STATISTICS

## 8.1. Sample Size Determination

With a total sample size of 70 subjects allocated in a 1:1 ratio between the treatment arm and placebo, the study will achieve at least 80% power to detect an effect size of 0.705 (assuming a treatment difference of 6.0 points in linearized total NSAA with common standard deviation of 8.5, or a treatment difference of 1.91 in raw total NSAA with common standard deviation of 2.71) in the mean change from baseline in the total NSAA -score with a one-sided significance level (alpha) of 0.025.

## 8.2. Analysis Populations

The analysis population is defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval.

### 8.2.1. Intent to Treat (ITT) Population

The ITT population is defined as all randomized subjects regardless of study treatment received. Subjects will be analyzed according to the treatment as randomized. The primary analysis of efficacy will be based on the ITT population.

### 8.2.2. Safety Population

The safety population is defined as all subjects who have received the study medication. Safety data will be summarized based on the Safety population. Subjects will be analyzed according to the treatment as received.

## 8.3. Statistical Analysis

### 8.3.1. General Considerations

The primary efficacy endpoint will be tested at the significance level of 0.05. Upon observing a significant treatment difference in the primary endpoint, the secondary endpoints will be tested taking into consideration the adjustment for the family-wise error-rate of 0.05. The fixed sequence testing procedure will be used for testing of the secondary endpoints in the order listed in section 3.2.2.

Efficacy and safety analyses for treatment comparisons will be based on data observed during the main study. Data from the OLE period will be summarized descriptively.

Treatment comparison will be based on data collected during double-blind placebo-controlled main study period. Descriptive summary will be provided for data during the open label extension.

Baseline characteristics, safety, efficacy and other data will be summarized by treatment arm based on available data in the ITT/Safety Population, except for the parameters specifically indicated otherwise.

Descriptive statistics for continuous variables include: n, mean, standard deviation or standard error, median, minimum, and maximum. Categorical variables will be presented by frequency counts of subjects and percentage. Two-sided 95% confidence intervals will be included for the key efficacy parameters.

### 8.3.2. Subject Enrollment and Disposition

The number (%) of subjects who completed or discontinued the study and reasons for early discontinuation will be summarized by treatment for subjects in the ITT population.

### 8.3.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for subjects in the ITT population.

### 8.3.4. Efficacy Analyses

#### 8.3.4.1. Analysis of Primary Endpoint Change in Total NSAA Score from Baseline to Week 52

The primary endpoint, change in the total NSAA Score, from baseline to Week 52 will be analyzed using a Mixed Model for Repeated Measure (MMRM) with treatment, visit visit-by-treatment interaction, randomization stratification, and baseline total score of NSAA, with an unstructured covariance matrix for the within subject covariance over time. The primary analysis will be based on observed data from subjects in the ITT population.

The analysis will take into account the potential intercurrent events as follows:

- Treatment discontinuation (such as: due to AEs, Lost to Follow-Up, Withdrawal by Subject, Physician Decision, Protocol Deviations, etc.): Treatment policy strategy: use all observed data, and missing data will be implicitly imputed under missing at random assumption.
- Death: Worst observation prior to death is imputed to Week 52

As sensitivity analysis, the analysis of covariance model (ANCOVA) model after multiple imputations (ANCOVA –MI) will be also applied. The model will include treatment, with randomization stratification and baseline total score of NSAA as covariates.

There will be 2 sets of multiple imputations performed for the missing data based on the two missing data pattern assumptions separately. One assumption of the missing data pattern is missing at random (MAR). Under the MAR assumption, the missing data after loss to follow-up will be imputed as continuing the trend of previously observed data, and this will be done separately for each treatment. The other missing pattern is missing not at random (MNAR). Under the MNAR assumption, the missing data after loss to follow-up for the pamrevlumab subjects will be imputed as having the same data distribution as those in the placebo group, and the missing data of the placebo subjects will be imputed as continuing the trend of previously observed data.

After a multiple imputation, the primary endpoint of change from baseline to week 52 total score of NSAA value will be calculated from the observed and imputed data and will be analyzed using analysis of covariance model (ANCOVA). The ANCOVA model will include the same covariates as in the primary analysis.

#### 8.3.4.2. Analyses of Secondary Endpoints

The following analyses will take into account the potential intercurrent events as follows:

- Treatment discontinuation (such as: due to AEs, Lost to Follow-Up, Withdrawal by Subject, Physician Decision, Protocol Deviations, etc.): Treatment policy for missing data will be implicitly imputed by the model under missing at random assumption.
- Death: Worst observation prior to death is imputed to Week 52.

##### 8.3.4.2.1. Changes in 4-stair climb Velocity (4SCV) assessment from baseline to Week 52

The change from baseline to week 52 in 4-stair climb velocity (4SCV) assessment will be analyzed, using a Mixed Model for Repeated Measure (MMRM) with treatment, visit, visit-by-treatment interaction, randomization stratification, and baseline 4-stair climb velocity (4SCV) assessment with an unstructured covariance matrix for the within subject covariance over time.

##### 8.3.4.2.2. Changes in 10M Walk/Run assessment from baseline to Week 52

The change from baseline to week 52 in 10-meter walk/run test will be analyzed, using a Mixed Model for Repeated Measure (MMRM) with treatment, visit, visit-by-treatment interaction, randomization stratification, and baseline 10-meter walk/run test with an unstructured covariance matrix for the within subject covariance over time.

##### 8.3.4.2.3. Changes in Time to Stand (TTSTAND) assessment from baseline to Week 52

The change from baseline to week 52 in time to stand (TTSTAND) will be analyzed, using a Mixed Model for Repeated Measure (MMRM) with treatment, visit, visit-by-treatment interaction, randomization stratification, and baseline time to stand (TTSTAND) with an unstructured covariance matrix for the within subject covariance over time.

##### 8.3.4.2.4. Time to Loss of ambulation (LoA), from baseline to Week 52

Time to loss of ambulation (LoA) will be summarized using the Kaplan-Meier method. The Cox proportional hazard model including treatment and randomization stratification factor will be used to compare the 2 treatment arms and to estimate the hazard ratio and the corresponding 95% confidence interval.

##### 8.3.4.2.5. Exploratory Analyses

###### 8.3.4.2.5.1. Change in fibrosis score of the lower extremities Vastus Lateralis muscle from baseline to Week 52, assessed by MRI

The change from baseline at week 52 in fibrosis score of the vastus lateralis muscle will be analyzed using a Mixed Model for Repeated Measure (MMRM) with treatment, visit, visit-by-treatment interaction, and baseline score as fixed effects, with an unstructured covariance matrix for the within subject covariance over time.

Exploratory endpoints, the change from baseline at week 52 in fibrosis score of lower extremities muscle will be analyzed using the same intercurrent handling and analysis method as for the primary endpoint.

#### 8.3.4.2.5.2. Changes in ppFVC and ppPEF from Baseline to Week 52

The Change from baseline to Week 52 in ppFVC will be analyzed using a Mixed Model for Repeated Measure (MMRM) with treatment, visit, visit-by-treatment interaction, and baseline ppFVC as fixed effects, with an unstructured covariance matrix for the within subject covariance over time.

The Change from baseline to Week 52 in ppPEF will be analyzed using a Mixed Model for Repeated Measure (MMRM) with treatment, visit, visit-by-treatment interaction, and baseline ppPEF as fixed effects, with an unstructured covariance matrix for the within subject covariance over time.

Exploratory endpoints, the change from baseline to Week 52 in ppFVC and ppPEF will be analyzed using the same intercurrent handling and analysis method as for the primary endpoint.

### 8.3.5. Pharmacokinetic Analyses

A population PK analysis will be defined in a separate plan.

### 8.3.6. Safety Analyses

All treatment-emergent adverse events (TEAEs) will be summarized by treatment arm, including: TEAEs Grade ≥3, treatment-emergent serious adverse events (TESAEs), deaths, and TEAEs leading to study or investigational product discontinuation.

Clinically significant changes from baseline in vital signs and laboratory tests will be summarized. Hypersensitivity/anaphylactic reactions will be monitored.

Additionally, the following safety analyses will be conducted:

- Number and percentage subjects with bone fractures.
- Annualized height velocity, HV (cm/year) from Baseline to Week 52

## 8.4. Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will include detailed analysis methods, statistical models, definitions, missing data handling as well as other data handling rules. It will document additional exploratory endpoints that are not specified in the protocol. The SAP will be finalized prior to database lock and treatment unblinding.

# 9. QUALITY CONTROL AND QUALITY ASSURANCE

## 9.1. Data Quality Assurance

Quality assurance and quality control systems will be implemented and maintained with Standard Operating Procedures by the Sponsor and its designee(s), as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, ICH E6 (GCP), and other applicable regulations.

This study will be monitored by the Sponsor or designee in accordance with GCP, and may be audited or reviewed by an independent Quality Assurance department, IRB/IEC, and/or regulatory authorities. This implies that monitors and auditors/inspectors will have the right to inspect the study sites at any time during and/or after completion of the study and will have direct access to data/source documents, including the subject's file. By participating in this study, investigators agree to this requirement.

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, IRT, 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).

Measures will be undertaken to protect the confidentiality of records that could identify subjects, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

## 9.2. Audit and Inspection

Authorized representatives of the sponsor, a regulatory authority, and/or an IRB/IEC may visit the investigator site to perform audits or inspections, including source data verification and source documentation review. The Investigator will allow the sponsor auditor (or designee), regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts (e.g. medical records) 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, ICH GCP guidelines, and any applicable regulatory requirements.

The investigator must contact the Sponsor, or its third party representative (CRO), immediately if notified by a regulatory authority of an inspection pertaining to this study.

# 10. ETHICS

## 10.1. Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirements, 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.

## 10.2. 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 as required by the policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required reports submitted to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen or designee. A copy of the signed FDA Form 1572 or other qualified investigator statement (as required) 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 or its designee. Written documentation of IRB/IEC approval must be received before the amendment is implemented.

Investigators must maintain a list of appropriate qualified persons to whom the investigator has delegated significant trial-related duties and update the list as staff and their delegated responsibilities change.

## 10.3. Subject Information and Consent

Prior to participation in any study-specific procedures, the subject must sign (note: all references to "subject" in this section refers to the study subject or their legally acceptable representative) an IRB/IEC-approved written Informed Consent Form (ICF) in their native language. The approved written informed consent must adhere to all applicable laws in regards to the safety and confidentiality of the subjects. To obtain and document informed consent, the investigator should comply with applicable regulations, and adhere to ICH GCP standards and the ethical principles in the Declaration of Helsinki (October 2008).

The language in the written information about the study should be as non-technical as practical and should be understandable to the subject. Before informed consent is obtained, the investigator should provide the subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written ICF should be signed and personally dated by the subject and the person who conducted the informed consent discussion, with any additional signatures obtained as required by applicable

local regulations and IRB/IEC requirements. Each subject will be informed that participation is voluntary and that he/she can withdraw from the study at any time. All subjects will receive a copy of the signed and dated ICF.

If there are any changes to the IRB/IEC approved 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, if/as required by the IRB/IEC.

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.

### 10.4. Subject Confidentiality

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

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.

The processing of personal data in pursuit of this study will be limited to those data that are reasonably necessary to investigate the utility of the study medications used in this study. These data will be processed with adequate precautions to ensure confidentiality according to local laws.

FibroGen ensures that the personal data are:

- collected for a specified and legitimate purpose
- processed fairly and lawfully
- accurate and up to date

Explicit consent for the processing of personal data will be obtained prospectively from the participating subject. FibroGen and/or designees whose responsibilities require access to personal data agree to keep the identity of study subjects confidential. This confidentiality will be maintained throughout the complete data processing.

Study subjects will be entitled to request confirmation of the existence of personal data held by FibroGen and will have the right to rectify erroneous or inaccurate data prior to database lock.

# 11. DATA HANDLING AND RECORD KEEPING

## 11.1. Source Documents

Source documents are original documents, data, and records necessary for the reconstruction and evaluation of the clinical study. The investigator or designee 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 Case Report Forms (CRFs) and resolved queries.

## 11.2. Direct Access to Source Documents

The investigator must provide direct access to source data and source documents for trial-related monitoring, audits, IRB/IEC review, and regulatory authority inspection. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to their study-related records, including personal information and medical records.

## 11.3. Data Collection, Handling, and Verification

All required data will either be entered into EDC by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory, or central imaging vendor). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations.

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) throughout the duration of the study and prior to study completion, ensuring that all data are verifiable with source documents.

DVA video data will be recorded by the caregiver in a secure, authenticated study mobile application and transmitted, using a secure Web service, to the mobile application database and encrypted. All media files received on the platform will be stored in an encrypted format. Data will be stored via secure data interchange and hosted on a secure Microsoft Azure server. Trained physical therapists will score the raw video data in a secure scoring dashboard, and de-identified scoring and video data will be transferred electronically to the sponsor or designee at predefined intervals during the study.

MFT video data will be recorded by the site user on a restricted pre-configured managed iPad, video data is then uploaded directly via HTTPS & TLS 1.2 to a secure web-based application and database which is encrypted using ASE256bit encryption. All data uploaded to the platform will be stored in an encrypted format. Data will be stored by a secure data interchange and hosted on a secure Amazon Web Services cloud servers within the European Union. Trained physical therapists will score the raw video data and de-identified scoring for accuracy of clinical evaluator performance. Video data will be uploaded to the secure web based application. Quality

reports will be available to the sponsor by access to a quality controlled report library. The Sponsor will have no access to de-identified videos and will not be transferred to the sponsor at any time.

### 11.4. Protocol Deviations

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the investigator or designee must document and explain the reason for any deviation from the approved protocol. The investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol violation or deviation to the IRB/IEC, the Sponsor, and to the regulatory authorities, if required.

### 11.5. Retention of Data

A Sponsor representative will inform the investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities, the Sponsoror designee, the investigator agrees to keep records, including the identity of all participating subjects (e.g. subject identification code list and all source documents), all original signed ICFs, copies of all CRFs, original laboratory reports, detailed records of drug disposition and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, the investigator may need to retain these documents for a longer period if required by applicable law, regulatory requirements or by an agreement with the Sponsor whichever is longer.

### 11.6. Financial Disclosure

The investigator's disclosable financial interests must be obtained prior to initiation of the study site, at completion of the study at the investigational site, and 1 year following study completion.

The investigator should promptly update this information if any relevant changes occur during the above described period.

Disclosable financial interests will be recorded on the investigator Financial Disclosure Form.

AnyiInvestigator(s) added as investigational staff to the form FDA 1572 or equivalent must complete the Investigator Financial Disclosure Form at the beginning of his/her participation in the study. The Investigator Financial Disclosure Form for any Investigator(s) leaving the clinical site prior to study completion will be obtained prior to study completion.

# 12. PUBLICATION POLICY

The data and results of the study will be owned solely by FibroGen and shall be confidential information of FibroGen, subject to the Investigator's publication rights, described below and if any outlined in the Clinical Trial Agreement. It is understood by the Investigator that FibroGen may use the information developed in this clinical study in connection with the development of its compounds and therefore, may disclose it as required to other clinical investigators, the Licensing Authority or to regulatory agencies of other governments. To allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide and disclose test results and all data developed during this study to FibroGen.

Any publication or presentation of the results of this clinical study by the Investigator may only be made in strict compliance with the provisions of the Clinical Trial Agreement. Any publication relating to the study shall be made in collaboration with FibroGen. The Investigator should understand that it is not FibroGen's intention to prevent publication of the data generated in the clinical study. However, FibroGen reserves the right to control the form and timing of such publication for commercial reasons. The Study Center and Investigator shall adhere to the publication language as outlined in both Clinical Trial Agreement and the protocol to the extent that if there is any conflict or ambiguity between Clinical Trial Agreement and the protocol, the publication terms in the Clinical Trial Agreement shall prevail.

# 13. REFERENCES

Annexstad EJ, Lund-Petersen I, Rasmussen M. (2014) Duchenne muscular dystrophy. Tidsskr Nor Laegeforen. 134(14):1361-1364.

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

Birnkrant DJ, Bushby K, Bann CM, et al. (2018) Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. The Lancet Neurology 17:347-361.

Bornstein P, Sage E (2002) Matricellular proteins: extracellular modulators of cell function. Curr Opin Cell Biol 14: (5):608

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

Bushby K, Muntoni F, Bourke JP. (2003) 107th ENMC international workshop: the management of cardiac involvement in muscular dystrophy and myotonic dystrophy. 7th-9th June 2002, Naarden, the Netherlands. Neuromuscul Disord. 13(2):166-172.

Buyse GM, Voit T, Schara U, Straathof CSM, D'Angelo MG, Bernert G, Cuisset JM, Finkel RS, Goemans N, McDonald CM, Rummey C, Meier T; DELOS Study Group. Efficacy of idebenone on respiratory function in patients with Duchenne muscular dystrophy not using glucocorticoids (DELOS): a double-blind randomised placebo-controlled phase 3 trial. Lancet. 2015 May 2;385(9979):1748-1757. doi: 10.1016/S0140-6736(15)60025-3. Epub 2015 Apr 20. PMID: 25907158.

Chen CC, Lau LF (2009) Functions and mechanisms of action of CCN matricellular proteins. Int J Biochem Cell Biol 41: (4):771-783

Connolly AM, Malkus EC, Mendell JR, et al. (2015) Outcome reliability in non-ambulatory boys/men with Duchenne muscular dystrophy. Muscle Nerve. 51(4):522-532.

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

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

Epstein AE, DiMarco JP, Ellenbogen KA, et al. (2008) ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 51(21):e1-62.

Falzarano MS, Scotton C, Passarelli C, et al. (2015) Duchenne muscular dystrophy: from diagnosis to therapy. Molecules. 20(10):18168-18184.

Finder J, Mayer OH, Sheehan D, et al. (2017) Pulmonary endpoints in Duchenne muscular dystrophy. A workshop summary. Am J Respir Crit Care Med. 196(4):512-519.

Kharraz Y, Guerra J, Pessina P, et al. (2014) Understanding the process of fibrosis in Duchenne muscular dystrophy. Biomed Res Int 2014:965631

Leung DG, Germain-Lee EL, Denger BE, et al. (2011) Report on the second endocrine aspects of Duchenne muscular dystrophy conference December 1-2, 2010, Baltimore, Maryland, USA. Neuromuscul Disord. 21(8):594-601.

Magrath P, Maforo N, Renella P, et al. (2018) Cardiac MRI biomarkers for Duchenne muscular dystrophy. Biomark Med. 12(11):1271-1289

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

McDonald CM, Henricson EK, Abresch RT, et al. (2018) Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 391(10119):451-461

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

Meier T, Rummey C, Leinonen M, et al. (2017) Characterization of pulmonary function in 10-18 year old patients with Duchenne muscular dystrophy. Neuromuscul Disord. 27(4):307-314

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

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

Pane M, Messina S, Bruno C, et al. (2013) Duchenne muscular dystrophy and epilepsy. Neuromuscul Disord. 23(4):313-315.

Perbal B. (2004) CCN proteins: multifunctional signalling regulators. Lancet 363: (9402):62-64

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

Porter JD, Merriam AP, Leahy P, et al. (2003) Dissection of temporal gene expression signatures of affected and spared muscle groups in dystrophin-deficient (mdx) mice. Hum Mol Genet 12:1813-21.

Rachfal AW, Brigstock DR (2005) Structural and Functional Properties of CCN Proteins. Vitam Horm 70:69-103

Ricotti V, Selby V, Ridout D, et al. (2019) Respiratory and upper limb function as outcome measures in ambulant and non-ambulant subjects with Duchenne muscular dystrophy: A prospective multicentre study. Neuromuscul Disord. 29(4):261-268

Sampson HA, Muñoz-Furlong A, Campbell RL, et al. (2006) Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 117(2):391-397.

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

Schwartz GJ, Schneider MF, Maier PS, et al. Improved equations estimating GFR in children with chronic kidney disease using an immunonephelometric determination of cystatin C. Kidney Int. 2012;82(4):445-453.

Seferian AM, Moraux A, Annoussamy M, et al. (2015) Upper limb strength and function changes during a one-year follow-up in non-ambulant patients with Duchenne Muscular Dystrophy: an observational multicenter trial. PLoS One. 10(2):e0113999.

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

Szigyarto CA, Spitali P. (2018) Biomarkers of Duchenne muscular dystrophy: current findings. Degener Neurol Neuromuscul Dis. 8:1-13

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

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

Tsuda T (2018) Clinical manifestations and overall management strategies for Duchenne muscular dystrophy. Methods Mol Biol. 1687:19-28

van Westering TL, Betts CA, Wood MJ. (2015) Current understanding of molecular pathology and treatment of cardiomyopathy in duchenne muscular dystrophy. Molecules. 20(5):8823-8855

Vial C, Zúñiga LM, Cabello-Verrugio C, et al. (2008) Skeletal muscle cells express the profibrotic cytokine connective tissue growth factor (CTGF/CCN2), which induces their dedifferentiation. J Cell Physiol. 215(2):410-421.

Walter MC, Reilich P. (2017) Recent developments in Duchenne muscular dystrophy: facts and numbers. J Cachexia Sarcopenia Muscle 8:681-685

Wu B, Cloer C, Lu P, et al. (2014) Exon skipping restores dystrophin expression, but fails to prevent disease progression in later stage dystrophic dko mice. Gene Ther. 21(9):785-793

Yiu EM, Kornberg AJ. (2015) Duchenne muscular dystrophy. J Paediatr Child Health. 51(8):759-764.

Zhou L, Lu H. (2010) Targeting fibrosis in Duchenne muscular dystrophy. J Neuropathol Exp Neurol.69(8):771-776

# 14. APPENDICES

## APPENDIX 1. SCHEDULE OF ASSESSMENTS

| | Screening | Treatment Period (Weeks)[a] | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (within 4 Weeks of Day 0) | Day 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 32 | 34 | 36 | 38 | 40 | 42 | 44 | 46 | 48 | 50 | 52 / EOT | Wk 56 28 days post last dose[j] | 60 days (+3 days) post dose (phone call)[j] |
| Informed Consent/ Assent | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Eligibility | X | X[l] | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Randomization | | X[l] | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Demographics | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Medical History | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Physical Exam[c] | X | | | | | | | X | | | | | | X | | | | | | X | | | | | | | | X | X | |
| Weight/Weight Based Adjustment[h] | X | | | | | | | X | | | | | | X | | | | | | X | | | | | | X | | | | |

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| PFTs (local)[k] | X | X[j] | | | | | | X | | | | | X | | | | | X | | | | | X | | | | | X | X[h] | |
| Vital Signs[d] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Chemistry & Hematology | X | | | | | X | | | | X | | | | X | | | | X | | | | X | | | | X | | | X | |
| 6MWD Test[n] | X | X | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | | | | | | | | | | | | | | | X | | |
| MFTs (NSAA, 4-Stair Climb Velocity, 10M Walk/Run, Time to Stand, LoA)[e] | X | X[j] | | | | | X | | | | | X | | | | | X | | | | | X | | | | | | X | X[b,h] | |
| Muscle MRI | X | | | | | | | | | | | | | | | | | | | | | | | | | | | X | X[h] | |
| PK (Optional) | | X | X | | | X | | | | X | | | | X | | | | X | | | | X | | | | X | | | X | |
| Specialty Lab: HAHAand HAHA-NA | | X | | | | | | | | | | | | X | | | | X | | | | X | | | | X | | | X[h] | |
| Duchenne Video Assessment[f] | | X | | | | | | | | | | | | X | | | | | | | | | | | | | | X | X[h] | |
| Pamrevlumab/ Placebo Infusion | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Adverse Events / SAEs[m] | X[g] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

Abbreviations: SAE = serious adverse event; EOS = End of Study; ET= Early Termination; HAHA = human anti-human antibody

a) Visit window of ± 3 days starting at Week 2

b) At the Early Termination visit, MFTs do not need to be repeated if the last one was performed within 4 weeks.

c) Full physical exam including chest auscultation

d) Vital signs (pulse, respiration, sitting BP, temperature) to be collected at every visit and twice during infusions (within 30 minutes prior to (pre-infusion), and within 30 minutes post-infusion.

e.) MFTs (NSAA, 4-Stair Climb Velocity, 10M Walk/Run, Time to Stand and Loss of Ambulation (LoA))

f) Duchenne Video Assessment to be performed remotely within the interval between the prior scheduled study visit and next scheduled study visit.

g) Only collecting SAEs prior to dosing

h) HAHA, HAHA-NA MRI, MFTs, PFTs, and Duchenne's video assessment only to be completed during the early termination visit

i) If the subject is not going into the OLE, he should complete a final safety follow-up that consists of a visit at week 56 and a final safety follow-up phone call 60 days (+3days) after the last infusion visit.

j) MFTs and PFTs are collected at screening and must be repeated prior to randomization and first infusion on Day 0. They may be conducted up to 3 days in advance of the Day 0 visit. The PFT results from both time points will be used to establish baseline values. The results from MFTs at Day 0 will be used to establish baseline.

k) PFTs include FVC, FEV1, and ppPEF to be done locally per the Institution's standards

l) Randomization may be performed within 2 days prior to Day 0 visit, after subject is confirmed eligible (see footnote "j").

m) SAEs are collected from date of consent through EOS. AEs are collected from Day 0 through EOS. Number and percentage of bone fractures is captured from Day 0 through EOS. Bone fractures should be collected in the EDC as AEs naming them using the CRF completion guidelines

n) Two 6MWD test results are needed within 3 months prior to Day 0 to establish eligibility prior to randomization (see Section 4.1). These tests may be conducted during the screening window, if historical results are not available.

## APPENDIX 2. PHARMACOKINETIC AND PHARMACODYNAMIC SAMPLING

| Timepoint P[a] | PK (Plasma) | HAHA[b] and HAHA - NA(Plasma) | Tryptase |
|---|---|---|---|
| Day 0 | X[c] | X[f] | |
| Week 2 | X[c] | | |
| Week 8 | X[c] | | |
| Week 16 | X[c] | | |
| Week 24 | X[c] | X[f] | |
| Week 32 | X[c] | X[f] | |
| Week 40 | X[c] | X[f] | |
| Week 48 | X[c] | X[f] | |
| Week 56/EOS or ET | X[d] | X[f] | |
| Immunogenic Reaction | X[e] | X[e] | X[e] |

**Abbreviations: PK = Pharmacokinetic; HAHA = human anti-human antibody; HAHA-NA = human anti-human antibody neutralizing antibody EOS = End of Study; ET = Early Termination;**

a.) For all time points, the actual date and time of sample collection must be recorded, in addition to date and time of study treatment administration.
b.) Separate samples for HAHA and HAHA-NA should be collected within 2 hours prior to the administration of study treatment. Samples/subjects with positive/specific HAHA results will be subject to evaluation of neutralizing antibody assay testing.
c.) Both Pre (within 2 hours prior to infusion start) and Post dose (between 1- 4 hours post infusion completion)
d.) Only one sample is required.
e.) PK, HAHA and HAHA-NA, tryptase sampling will be required following the immunogenic reaction. **NOTE:** Local guidance and regulations on the maximum allowable total blood volume should be followed. Please review your lower weight patients (see section 6.2.4.3 for more details).
f.) While samples for HAHA and HAHA-NA are drawn for all subjects, only samples/subjects with positive/specific HAHA results will be subject to neutralizing antibody (HAHA-NA) testing.

## APPENDIX 3. NORTHSTAR AMBULATORY ASSESSMENT (NSAA)

The NorthStar Assessment (NSAA) worksheet should be used to document the scores for the assessments. A separate manual will be provided as a guide on how the tests should be conducted. Note: The Time to Stand test is called Rise from Floor and is contained within the NSAA.

| Activity | 2 | 1 | 0 | Score |
|---|---|---|---|---|
| **1. Stand** *3 | Stands upright, still, symmetrical, without compensation (heels flat and hips in neutral rotation) for minimum count of 3 seconds | Stands still but with compensation (e.g. on toes or with legs abducted or with bottom stuck out/hip flexion, etc.) for minimum count of 3 seconds | Cannot stand still or cannot stand independently, needs support (even minimal) | |
| **2. Walk** *3 | Walks consistently with heel-toe or flat-footed gait pattern | Persistent or habitual toe walker, unable to heel-toe consistently | Loss of independent ambulation – may use knee-ankle-foot orthosis (KAFO) or walk short distances with assistance | |
| **3. Stand up from chair** *3 | Able to stand up keeping arms folded | With help from thighs / push on chair / prone turn or alters starting position by widening base (moving feet apart) | Unable | |
| **4. Stand on one leg – right** *3.5 | Able to stand upright in a relaxed manner (no fixation) for a count of 3 seconds | Stands but either momentarily or with trunk side-flexion (20◦) or needs fixation e.g. by thighs adducted | Unable | |
| **5. Stand on one leg – left** *3.5 | Able to stand upright in a relaxed manner (no fixation) for a count of 3 seconds | Stands but either momentarily or with trunk side-flexion (20◦) or needs fixation e.g. by thighs adducted | Unable | |
| **6. Climb box step – right** *3 | Faces step – no support needed | Goes up sideways / rotates trunk / circumducts hip / needs hands for balance or hands on legs | Unable to perform independently | |
| **7. Descend box step – right** *3.5 | Faces forward, steps down controlling weight-bearing leg. No support needed | Sideways / skips down / needs hands for balance or hands on legs | Unable without more than minimal support, or requires hands for support | |
| **8. Climb box step – left** *3 | Faces step – no support needed | Goes up sideways / rotates trunk / circumducts hip / needs hands for balance or hands on legs | Unable to perform independently | |
| **9. Descend box step -left** *3.5 | Faces forward, steps down controlling weight-bearing leg. No support needed | Sideways / skips down / needs hands for balance or hands on legs | Unable without more than minimal support, or requires hands for support | |
| **10. Lifts head** *4 | In supine, full neck flexion, head must be lifted in mid-line. Chin moves towards chest | Head is lifted through side flexion, partial neck flexion, or with protraction | Unable. No clearance of head from surface | |
| **11. Gets to sitting** *3 | Starts in supine – may use one hand / arm to push up | Uses two arms / pulls on legs or turns towards floor or uses momentum/rocking | Unable | |

| | | | | |
|---|---|---|---|---|
| **12. Rise from floor** *4 | No evidence of Gower's manoeuvre. | Exhibits at least one of the components described above – in particular rolls towards floor, and/or use hand(s) on legs | (a) NEEDS to use external support object e.g. chair, wall OR (b) Unable NO TIME RECORDED | |
| **13. Stands on heels** *3.5 | Both feet at the same time, clearly standing on heels only (acceptable to move a few steps to keep balance) for count of 3 | Raises forefoot on both feet – all metatarsal heads off ground – or clearly dorsiflexes one foot only | Unable | |
| **14. Jump** *3 | Both feet at the same time, clear the ground simultaneously and land at the same time | One foot after the other (skip) or does not fully clear both feet at the same time | Unable | |
| **15. Hop right leg** *4 | Entire foot clears the floor | Able to bend knee AND raise heel, no floor clearance | Unable or only raises heel | |
| **16. Hop left leg** *4 | Entire foot clears the floor | Able to bend knee AND raise heel, no floor clearance | Unable or only raises heel | |
| **17. Walk Run** (10 m) *3 | Both feet off the ground (no double stance phase during running) | 'Duchenne jog' or fast walk | Walk | |
| | | | **TOTAL=** | **/34** |

**Timed RFF:** no time if uses furniture _____.____ **Timed 10m run / walk** _____.____

Age at which 85% of controls achieve full score *3 = 3 years of age, *3.5 = 3.5 years of age, *4 = 4 years of age (Mercuri 2016)

## APPENDIX 4. OPEN LABEL EXTENSION (OLE)

This is an optional open-label, single arm extension to evaluate long-term efficacy and safety of pamrevlumab in DMD subjects. Subjects who complete week 52 of the main study (regardless of the number of study drug infusions received) will be eligible to participate in the open-label, extension (OLE) where all subjects will be treated with pamrevlumab. After completing Week 52 of the main study, participants electing to go into the OLE will move to Week 2 of the OLE. The EOS visit will be completed at the end of participation in the OLE. If a subject discontinues the main study early for any reason, they will not be eligible for inclusion in the OLE.

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 a final follow-up 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. All subjects will receive pamrevlumab in an open-label manner. Note: No unblinding of subject's treatment assignment in the main study will occur for purposes of OLE participation.

The following conditions are excluded for continued participation in this OLE phase:

- Use of any investigational drugs, or participation in a clinical trial with an investigational new drug, other than participation in the main study.
- History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies, or experienced an allergic or anaphylactic reaction to study drug or any component of study drug.
- Subjects who withdrew informed consent while participating in the main study, or who discontinued early from the main study for any reason.
- The Investigator judges that the subject is not suitable for participation, or is unable to fully participate in the OLE phase and complete it for any reason, including inability to comply with study procedures and treatment, or any other relevant medical or psychiatric conditions

### 1. Endpoints

**Ambulatory functional assessments:**

- Change in NorthStar Ambulatory Assessment (NSAA) total score.
- Change in 4-stair climb Velocity (4SCV) assessment.
- Change in the 10-meter walk/run test.
- Change in Time to Stand (TTSTAND).
- Change of the time of Loss of Ambulation (LoA) assessment

**Safety assessments**

- Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), clinically significant laboratory test abnormalities, and discontinuation of treatment due to TEAEs serve as the safety assessments for this OLE.
- Number and percentage of subjects with hospitalizations due to any serious adverse events with pulmonary and/or cardiac cause(s),
- Number and percentage of subjects with bone fractures.
- Annualized height velocity from Baseline of OLE to Week 52 of OLE

## 2. Study Enrollment

All subjects participating in the Open Label Extension must have completed treatment through the primary endpoint and completed the Week 52 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/IEC) must be obtained prior to the subject's participation in the OLE. Administration of currently 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 and Assessments

All study visits will be performed in accordance with the Schedule of Assessments presented in Section 5.

- The dosing period starts 14 days (±3 days) after the parent study at the Week 52 visit. Subjects should be consented and eligibility confirmed during the Week 52 visit of the main 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

  Missed doses are not to be made up through extra visits. If a subject misses more than two infusions in an 8 week period, or two sequential infusions, the FibroGen Medical Monitor should be notified. The reason for missed doses must be documented in the subject's clinical record.
- Vital signs (pulse, respiration, sitting BP, temperature) to be collected at every infusion visit: within 30 minutes pre-infusion, and within 30 minutes after completion of infusion. Physical exams should be performed in accordance with local standard of care (i.e., every 24 weeks). Any significant findings will be reviewed by the Investigator to determine appropriate reporting of adverse events.
- Muscle function tests including Loss of Ambulation (LoA) will be performed every 12 weeks MFTs 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. Video QC will not be required during the OLE.

- Weight will be performed every 12 weeks to make any weight based dose adjustments for the next 12 week period. Weight can be performed up to 2 weeks in advance of the 12 week interval visit.
- Chemistry and hematology tests (Chemistry panel, CBC with differentials, and liver function tests (LFTs)) should be completed centrally very 24 weeks. Lab results should be reviewed by the Investigator for clinically significant abnormalities and determine appropriate reporting of adverse events. A specialty lab will perform PK, HAHA, and HAHA-NA testing for each specified blood draw timepoint in the OLE. PK testing is not optional in the OLE.Any immunogenic reactions, including drug-related hypersensitivity or anaphylaxis, should have PK, HAHA, HAHA-NA drawn within 24 hours of reaction. (A window of "within 24 hours of reaction" could be at any point following the reaction such as 30 minutes post-reaction but not to exceed 24 hours following reaction). The Tryptase sample should be drawn within 1 to 6 hours of immunogenic reaction, but all samples should at least be collected within 24 hours after the anaphylactic episode. For study visits in which PK, HAHA, and HAHA-NA were drawn as part of the Schedule of Assessments, if an Immunogenic reaction occurs, additional samples still need to be taken within 24 hours of the immunogenic reaction. This will not be considered optional for the subject unless there is local consideration for total blood volume collection on the same day as a standard blood draw timepoint, which could preclude the subject from having this collection take place within 24 hours. See Appendix 2 for more detail.
- NOTE: Patients that have an immunogenic reaction that occurs on the same date as a routine study blood draw and weigh less than 30kg, must wait 24 hours prior to drawing the corresponding PK, HAHA, HAHA-NA, and tryptase for immunogenicity per general guidance on the lower limit total blood volume. However, local guidance and regulations should be consulted regarding total blood volume to be drawn within a certain time frame and takes precedence over any general recommendations.
- Any assessments repeated as a part of main study, and all AEs prior to first dose in OLE are considered as a part of the main study.

Subjects who complete the dosing period or early terminate will have a final follow-up visit 4 weeks (±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.

**Home Health Care**

During the OLE, the first three doses of the investigational product (IP) infusion must be administered at the study site. Home infusions for subsequent infusions may be an option as in the main study on a case by case basis as requested by the study site in geographic areas where such service could be feasibly provided.

## 4. Statistical Considerations

Data collected during the extension period will be summarized descriptively along with the main study.

**5. OLE Schedule of Assessments**

| | Q2 WEEKS (± 3 days) | Q12 weeks (± 3 days) | Q24 weeks/EOT (± 3 days) | Final Safety Follow-up (4 Weeks (± 3 days) after Last treatment) EOS/ET | Final Safety Phone Call (60 Days (+3 days) after last treatment) |
|---|---|---|---|---|---|
| Informed Consent & Assent/Eligibility[a] | | | | | |
| Vital Signs[b] | x | x | x | x | |
| Chemistry & Hematology (Central Labs) | | | x | x | |
| Muscle Function Tests[d] | | x | x | x[c] | |
| Physical Examination | | | x | x | |
| Weight/Weight Based Dose Adjustment | | x[f] | x[f] | | |
| Height | | | x | | |
| Specialty Labs (PK, HAHA, and HAHA-NA) | | | x | x | |
| Pamrevlumab Infusion | x | x | x | | |
| AEs / SAEs[g] | x | x | x | x | x |
| Concomitant Medications | x | x | x | x | x |

Abbreviations: AE = adverse event; EOS = End of Study; EOT = End of Treatment; ET= Early Termination;

a. Prior to starting infusions and procedures for the OLE, subject must sign the OLE consent and be confirmed eligible at the Week 52 visit of the main study.
b. Vital signs (pulse, respiration, sitting BP, temperature) to be collected at every visit: within 30 minutes pre-infusion, and within 30 minutes after completion of infusion. For EOS/ET, vitals to be completed one time only.
c. Completed at the Early Termination visit only, MFTs do not have to be repeated if the last one was conducted within 8 weeks of this visit.
d. Muscle Function Tests (MFTs): NSAA, 4SCV, 10M walk/run, TTSTAND, and Loss of Ambulation (LoA)
e. Weight should be measured every 12 weeks to determine dose for the subsequent 12-week interval. Weight for dose adjustments can be collected up to two weeks in advance.

PK, HAHA and HAHA-NA sampling required at all blood draw visits in the OLE. PK is not optional in the OLE. See **Appendix 2** for more details on immunogenic reaction blood draws.

Signature Page for VV-CLIN-013270 v1.0

| | |
|---|---|
| Approval Task | [redacted]<br>09-Nov-2022 15:06:58 GMT+0000 |

Signature Page for VV-CLIN-013270 v1.0