Study FGCL-3019-079

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

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FIBROGEN

Pamrevlumab (FG-3019) Background
Pamrevlumab (FG-3019): a novel investigational agent for treating fibrotic and fibro-proliferative diseases

- 11 Phase 1 and Phase 2 clinical trials completed or ongoing
  - To date over 550 patients have been enrolled in pamrevlumab clinical studies
  - Over 450 patients have received pamrevlumab
  - About half of the patients have received treatment for > 6 months

- Safety
  - No safety signals have been seen to date that might prevent further development of the drug
    - Well tolerated and no dose limiting toxicities
    - Adverse events have generally been mild or moderate

- Proof of concept in pulmonary fibrosis and pancreatic cancer
Pamrevlumab Background (cont.)

Pamrevlumab: a novel investigational agent for treating fibrotic and fibro-proliferative diseases

Fully human monoclonal antibody to connective tissue growth factor (CTGF) a central mediator of fibrosis

• **Idiopathic pulmonary fibrosis (IPF)**
  – Completed a one year open-label Phase 2 trial in 89 patients showing some reversal of lung fibrosis and improved lung function (*Eur Respir J* 2016; 47: 1481–1491)
  – Conducting a randomized placebo-controlled Phase 2b trial with 160 patients

• **Pancreatic cancer**
  – Completed Phase 1/2 trial in 75 patients showing dose-related improvement in survival (*J Cancer Clin Trials* 2017, 2:1)
  – Ongoing Phase 1/2 trial in 42 patients with locally advanced disease
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Pamrevlumab Rationale for Treatment of DMD
DMD is a Fibrotic Disease

In DMD, repeated cycles of muscle degeneration and regeneration lead to replacement of dystrophic muscle by fibrotic tissue and fat.

Slowing or reversal of fibrosis is expected to slow or reverse loss of muscle function.
Blockade of CTGF with Pamrevlumab May Impact Fibrosis

Normal Wound Healing

- Regeneration of damaged tissues
- MMP-TIMP balance restored
- Wound contraction and re-epithelialization
- Remodeling and maturation phase

Fibrosis

- Excessive EGM deposition
- Chronic injury, inflammation, or necrosis
- Persistent myofibroblast activation
- Collagen and fibronectin

Pamrevlumab (FG-3019)

Excess CTGF

Adapted from: Wynn J Clin Invest. 2007; 117:524-9
Blockade of CTGF with Pamrevlumab May Reduce Muscle Fibrosis

Pamrevlumab Treatment

↓ Vascularity  ↓ Fibrosis  ↓ Endogenous regeneration

↑ Vascularity  ↓ Fibrosis  ↑ Endogenous regeneration
Rationale for Pamrevlumab as a Treatment for DMD

CTGF

- Associated with fibrotic responses of many organs
- Elevated in human DMD and in animal models of the disease
- Has been shown to induce a dystrophic phenotype in normal animals

*mdx mouse model* of DMD

- Pamrevlumab treatment attenuated tissue damage, fibrosis and loss of muscle strength, and increased exercise stamina in an mdx study

Hypothesis is that inhibition of fibrosis in DMD with pamrevlumab may:

- Increase the contractile capacity of dystrophic muscles
- Slow disease progression in DMD patients

Goal of trial is to estimate pamrevlumab’s efficacy and safety in non-ambulatory patients with DMD

* The *mdx* mouse study was repeated in an independent laboratory. Observations made in the original study were not reproduced.
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Protocol Overview

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

Open-label, single-arm study of up to 22 non-ambulatory boys age 12 years and older

- Currently enrolling
  - Each patient will receive pamrevlumab (FG-3019) by IV infusion every 2 weeks for up to 52 weeks (Initial Phase). T\n  - Patients that achieve a $\leq 5\%$ decline from baseline in FVC % predicted by Week 52, will qualify to move forward to Extended Treatment phase of 26 weeks
  - The treatment duration, including extension treatment, is 78 weeks

• This study will be amended to extend treatment period to 104 weeks (2 years)
Trial Objectives

Objectives

– To estimate efficacy, evaluate safety and tolerability, and assess pharmacokinetics (PK) of pamrevlumab (FG-3019) in non-ambulatory boys with DMD aged 12 years and older

Efficacy Endpoints

– Change in pulmonary function: forced vital capacity, maximum inspiratory flow, maximum expiratory pressure and peak expiratory flow, peak cough flow

– Change in upper body muscle function tests: Performance of Upper Limb (PUL), grip strength, pinch strength, Brooke Score

– Change in muscle fibrosis and/or fat by MRI imaging of biceps

– Change in cardiac fibrosis and function by MRI imaging
Key Inclusion Criteria

• At least 12 years of age
• Non-ambulatory
• Brooke Score for Arms and Shoulders ≤5
• Diagnosis of DMD by medical history and confirmed Duchenne mutation in available genetic testing using a validated genetic test
• Able to perform spirometry
• Able to undergo cardiac and extremity (upper arm) MRI
• Percent predicted FVC between 40 and 90, inclusive
• At least one historical FVC % predicted value within 18 months of baseline
• Left ventricular ejection fraction >45% as determined by cardiac MRI at screening or within 3 months prior to Day 0
• Patients currently receiving heart failure cardiac medications must achieve a stable regimen for at least 3 months prior to screening
• On a stable dose of corticosteroids for a minimum of 6 months, with no substantial change in dosage for a minimum of 3 months
Key Exclusion Criteria

- Requires ≥16 hours continuous ventilation
- Anticipated spine surgery within 78 weeks
- Severe uncontrolled heart disease including any of the following:
  - Need for IV diuretics or inotropics within 3 months prior to screening
  - Hospitalization for a heart failure exacerbation or arrhythmia in last 3 months
- Arrhythmia requiring anti-arrhythmic therapy
- Hospitalization due to respiratory failure in the last 6 weeks
- Poorly controlled asthma or underlying lung disease such as bronchopulmonary dysplasia
- BMI ≥40 kg/m² or weight >117 kg
- Exposure to another investigational drug or approved product for DMD within 28 days prior to start of study treatment with the exception of deflazacort
Clinic Visits

- Visit to clinics every 2 weeks
  - Each study visit will typically take 2 - 3 hours (4 - 6 hours when both infusions and assessments are scheduled)
  - Procedures/Assessments:
    - IV Study Drug Infusion every 2 weeks (35 mg/kg)
    - Blood draws every 2 weeks for Safety
    - Physical exam, vital signs, weight and height
    - Muscle Function Tests
    - Pulmonary Function Tests
    - Cardiac and Upper Arm MRI
    - Electrocardiogram (ECG)
    - Quality of Life Questionnaire
    - Additional Blood Draws for PK
Participating Centers

- Cincinnati Children’s in Cincinnati, OH
- Washington University in St. Louis, MO
- UCSF Benioff Children's Hospital in San Francisco, CA
- Children’s Hospital Colorado in Aurora, CO
- University of Iowa Children’s Hospital, Iowa City, IA
- Children’s Hospital in Philadelphia, PA
- Boston’s Children’s Hospital in Boston, MA
- Shriner’s Hospital for Children in Portland, OR
- UCLA School of Medicine in Los Angeles, CA
- Children’s Medical Center in Dallas, TX
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- Extend our appreciation to patients, their families and the DMD community

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- Acknowledge the participation of our investigators
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Questions