**Phase 1/2 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Effects of AOC 1020 Intravenously to Adult Patients with Facioscapulohumeral Muscular Dystrophy (FORTITUDE™) Trial Design**

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**Background**

- Facioscapulohumeral dystrophy (FSHD) is one of the most common forms of muscular dystrophy affecting approximately 14,000–30,000 people in the US.
- FSHD is an autosomal dominant disease caused by abnormal expression of double homeobox 4 (DUX4), leading to a series of downstream events that result in skeletal muscle degeneration and wasting (Figure 1A).
- Current medical treatment is focused on symptom management and pain, anxiety, depression, and fatigue.

**Mechanism of Action**

- **Figure 1** illustrates the structure of AOC 1020 and its three components:
  1. **TREATMENT APPROACH**
  2. **Oligonucleotide:** Stabilized siRNA targeting DUX4 mRNA (siDUX4) designed to target and degrade DUX4 mRNA.
  3. **Non-cleavable linker:** Humanized IgG1 monoclonal antibody (hAV01mAb) engineered to target skeletal muscle.

**Trial Objectives and Endpoints**

**Primary Objective**
- Evaluate safety and tolerability of AOC 1020

**Secondary Objective**
- Evaluate PK (pharmacokinetics) of AOC 1020

**Key Biomarker Objectives**
- Evaluate effects of AOC 1020 on PK biomarkers and clinical endpoints (12 months)

**Key Exploratory Objectives**
- Evaluate effects of AOC 1020 on PD biomarkers and clinical endpoints

**Key Exploratory Clinical Endpoints**
- Total muscle volume, muscle fat fraction, muscle fat infiltration
- DUX4 regulated gene panel

**Key Exploratory Clinical Endpoints**
- Reachable Workspace (RW)
- Functional mobility endpoints
- Time to second/second
- Strength measurements
- Hand-held dynamometry
- PR6 to assess upper body function, quality of life, sleep, pain, anxiety, depression, and fatigue

**Abbreviations**

AOC, antibody oligonucleotide conjugate; BMI, body mass index; DUX4, double homeobox 4; FCS, FSHD clinical score; FORTITUDE, FSHD Treatment of FSHD; MRI, magnetic resonance imaging; mRNA, messenger RNA; OLE, open-label extension; PRO, patient-reported outcomes; RWS, reachable workspace; siRNA, small interfering RNA; TTR, human transferrin receptor;