Trial design for the Phase 2 FORGE study evaluating apitegromab in adults with facioscapulohumeral muscular dystrophy

Poster #P2.10

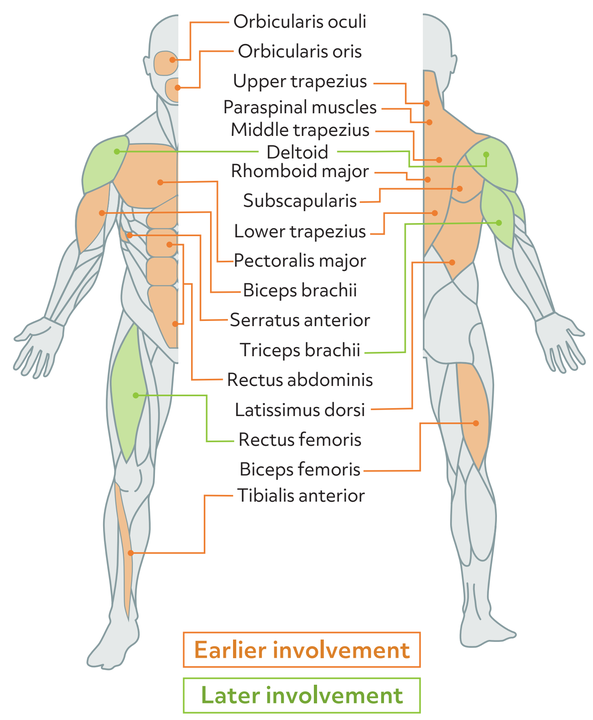
Jeffrey M. Statland,[1] Nicholas E. Johnson,[2] John Vissing,[3] Ryan A. Frieler,[4] Guochen Song,[4] Jing L. Marantz,[4] Leslie Nelson,[5] Tina Duong,[6] John Staropoli[4]

[1]The University of Kansas Medical Center, Kansas City, KS, USA; [2]Virginia Commonwealth University School of Medicine, Richmond, VA, USA; [3]Copenhagen Neuromuscular Center, Copenhagen, DK; [4]Scholar Rock, Cambridge, MA, USA; [5]University of Texas Southwestern Medical Center, Dallas, TX, USA; [6]Stanford University, Palo Alto, CA, USA

INTRODUCTION

- Facioscapulohumeral muscular dystrophy (FSHD) is a rare primary myopathy characterized by progressive and often asymmetric weakness of the facial, shoulder, and lower limb muscles (**Figure 1**)[1,2]
- Apitegromab is an investigational, fully human monoclonal antibody that inhibits the activation of mature myostatin, a negative regulator of muscle mass, by selectively binding with high affinity to promyostatin and latent myostatin (**Figure 2**)[3-5]
- In clinical studies for patients with spinal muscular atrophy (SMA) (Phase 2 TOPAZ, NCT03921528; Phase 3 SAPPHIRE, NCT05156320), apitegromab was generally well tolerated and provided substantial motor function gains across a broad range of patients who were concurrently receiving survival motor neuron-targeted treatment[5-7]
- Preclinical studies of the apitegromab murine analog (muSRK-015) in a FLExD model of FSHD demonstrated significant increases in skeletal muscle mass, muscle force, and endurance[8]

Figure 1. Early and late skeletal muscle involvement in FSHD[1,2]



FSHD, facioscapulohumeral muscular dystrophy.
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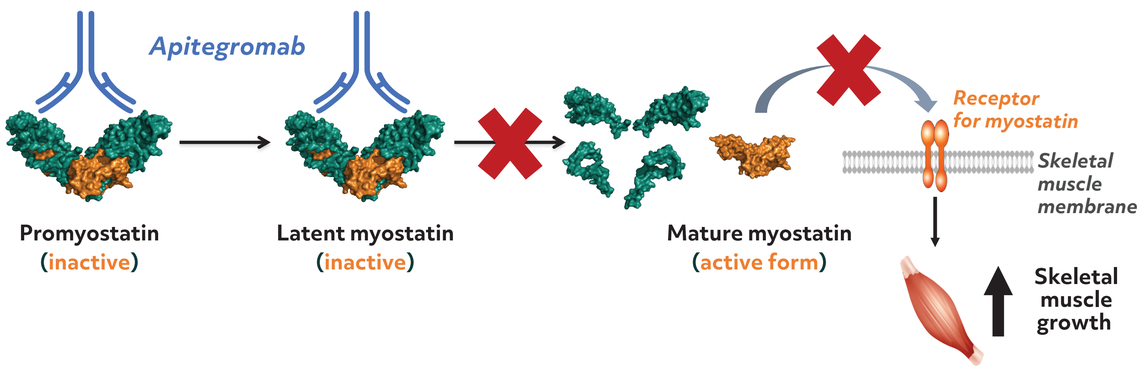
Figure 2. Apitegromab mechanism of action[3-5]



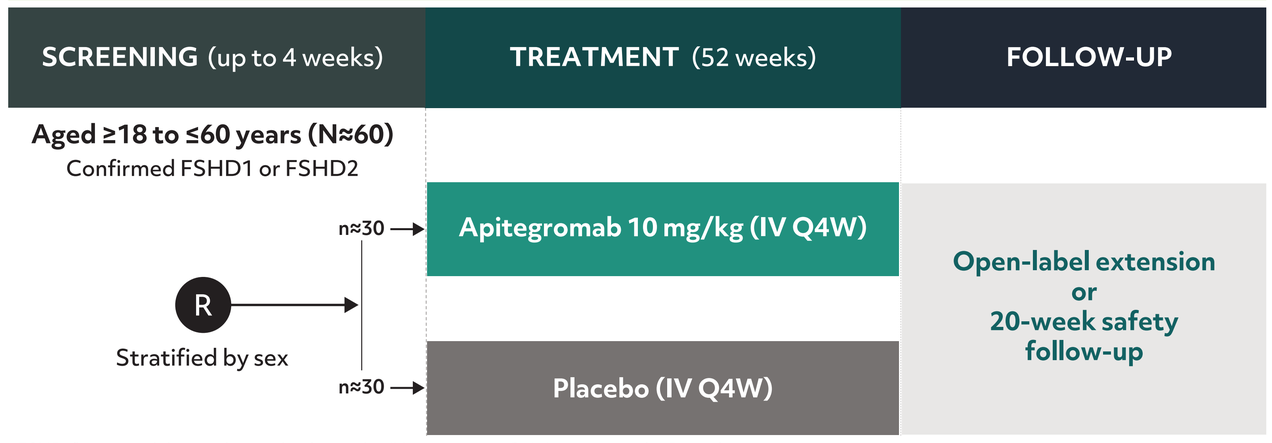
OBJECTIVE

- The planned Phase 2 FORGE trial (NCT07435129) aims to assess the efficacy, pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of apitegromab monotherapy in ambulatory adults with FSHD

METHODS

- FORGE is a Phase 2, double-blind, randomized, placebo-controlled, multicenter trial of apitegromab treatment in ambulatory adults with FSHD (**Figure 3**)
  - This trial will include a screening period of up to 4 weeks and a 52-week treatment period (13 doses), followed by either participation in an open-label extension trial or a 20-week safety follow-up period
- Approximately 60 participants will be randomized 1:1 to receive 10 mg/kg apitegromab monotherapy or placebo by intravenous infusion every 4 weeks (Q4W)
  - The clinical dose of apitegromab 10 mg/kg Q4W is supported by clinical efficacy and safety data in SMA[5] and PK/PD and exposure-response modeling in healthy participants and patients with SMA[9-11]
- This trial is expected to be conducted across 20 sites in North America and Europe
- Key eligibility criteria include age ≥18 to ≤60 years, confirmed genetic diagnosis of FSHD1 or FSHD2, a Ricci clinical severity score of 1.5 to 3.0, and a baseline 10-meter walk/run test time of ≤5 seconds (**Table 1**)
- Primary, secondary, and select exploratory endpoints are listed in **Table 2**
- The second half of the study (Week 24 to Week 52) will include a standardized at-home strength training regimen

Figure 3. Trial design



FSHD, facioscapulohumeral muscular dystrophy; IV, intravenous; Q4W, every 4 weeks; R, randomization.

Table 1. Key eligibility criteria

Key inclusion criteria	Male or female participants aged ≥18 to ≤60 years
	Genetically confirmed diagnosis of FSHD1 or FSHD2
	Clinical severity score of 1.5 to 3.0 (Ricci score: range 0-5)
	Baseline 10MWRT time ≤5 seconds
Key exclusion criteria	Any medical condition, clinically significant laboratory result, or ECG value that may compromise safety, interfere with study compliance, or confound the interpretation of results
	Current or prior use of anabolic steroids, growth hormones, GLP-1 receptor agonists, or other substances with known effects on muscle
	Use of systemic corticosteroids or therapies with potentially significant muscular or neuromuscular effects within 60 days of screening
	Previous treatment with apitegromab or with other antimyostatin therapies, including activin receptor antagonists
	Treatment with other investigational drugs in a clinical study within 3 months or 5 half-lives, whichever is longer, before screening

10MWRT, 10-meter walk/run test; ECG, electrocardiogram; FSHD, facioscapulohumeral muscular dystrophy; GLP-1, glucagon-like peptide-1.

Table 2. Primary, secondary, and select exploratory endpoints

Primary endpoint	• Percent change from baseline in total LMV (as measured by full-body MRI) at Week 52
Secondary endpoints	• Percent change from baseline in total LMV (as measured by full-body MRI) at Week 24 • Change from baseline in additional muscle parameters at Week 24 and Week 52 • Serum concentrations of apitegromab (PK) and total latent myostatin (PD) • Incidence of AEs and SAEs • Incidence of antidrug antibodies
Select exploratory endpoints	• Change from baseline in QMT • Change from baseline in RWS • Change from baseline in FSHD-COM

AE, adverse event; FSHD-COM, Facioscapulohumeral Muscular Dystrophy–Composite Outcome Measure; LMV, lean muscle volume; MRI, magnetic resonance imaging; PD, pharmacodynamics; PK, pharmacokinetics; QMT, quantitative muscle testing; RWS, reachable workspace; SAE, serious adverse event.

CONCLUSIONS

- The Phase 2 FORGE trial will be the first to evaluate apitegromab, a muscle-targeted treatment, in adults with FSHD

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Email: medicalinformation@scholarrock.com