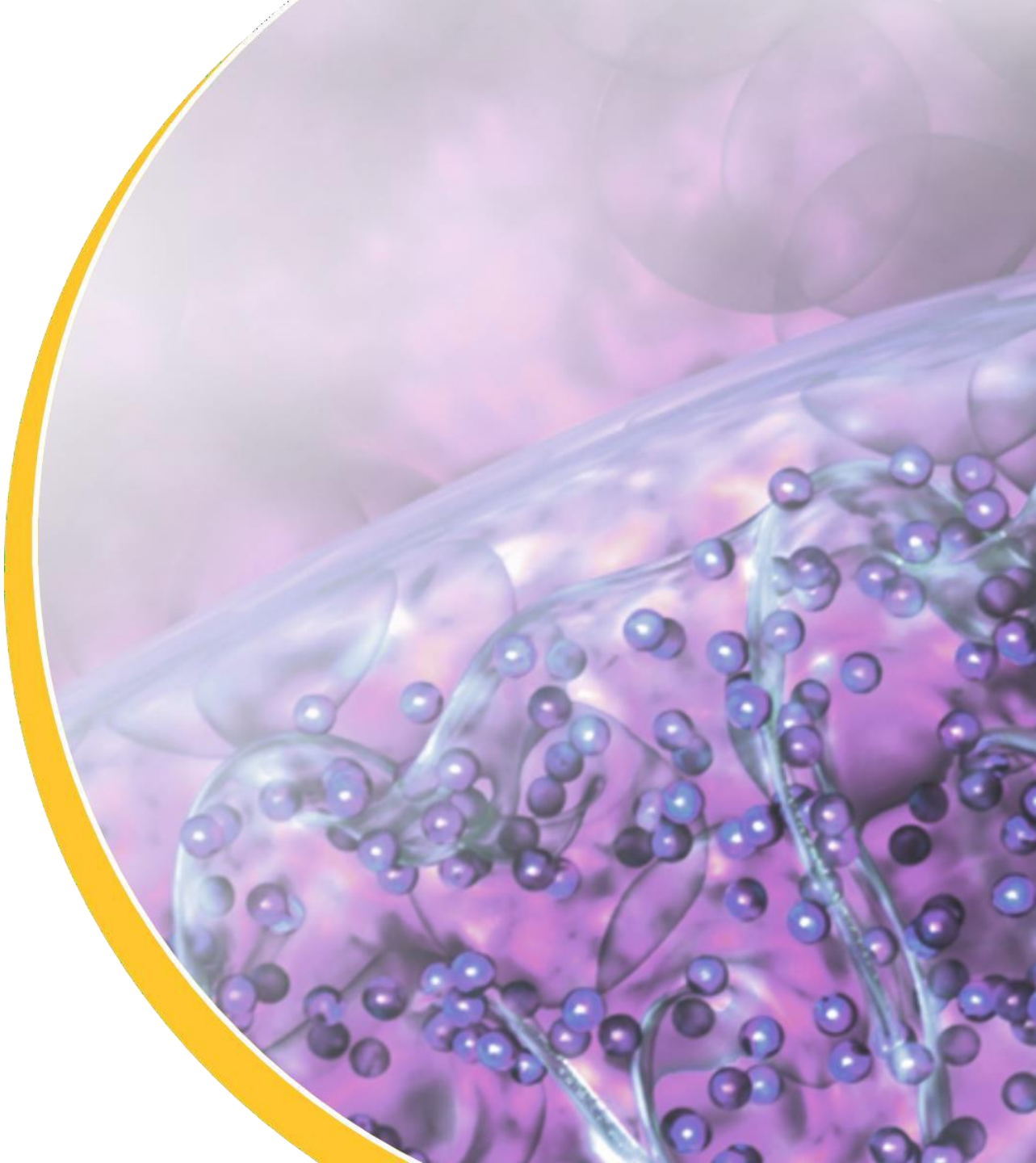
Epirium Bio

## Novel Platform: Pipeline in a Mechanism, Oral Treatments for Neuromuscular Diseases

- **MF-300 "First-in-Class" Oral Therapy for Sarcopenia**
- **Additional High Value Opportunities**:
  - Sarcopenic Obesity & Neuromuscular Disease



# Experienced Team with a Demonstrated Track Record of Success

## Epirium Leadership Team

### Alex Casdin, CEO

25+ year track record success in biotech & healthcare:

Port. Mgr: Pequot Capital; CEO & PM: Cooper Hil Partners, Reneo Capital

VP Finance, Amylin; CFO, Sophiris

Investor, Board Member & Audit Chair – Ignyta (acq. Roche), Erasca;

Board: Dusa (acq. Sun Pharma) , 454 Life Sciences (acq. Roche)

### Eric Miller, CFO

Synthorx (acq. Sanofi)

Acadia Pharm -Commercial Stage

Cadence Pharm. (acq. by Mallinckrodt)

### Micah Webster, Sr. Director, TS

Ph.D. Cellular and Molecular Biology, JHU

Scholar Rock, Associate Director, Translational Science

Discovery programs & Biomarker Strategy for apitegromab

## Key Consultant Advisors

### Leigh MacConnell, Ph.D. Clinical Development

25 years drug development, primarily in metabolic and liver disease

Led multiple drug approvals including first in class for T2DM (GLP-1) and Primary Biliary cholangitis (FXR agonist)

Successfully worked with FDA to define drug approval pathways for disease areas without prior regulatory precedence including NASH

### Elaine Chiquette, Pharm.D. Scientific Affairs

C-Suite executive with 20+ years experience in pharma, biotech, and medical device

Led regulatory approvals for NDA, BLA, PMA across USA, EU and China

Formerly served as CSO and head of regulatory & medical affairs at Gelesis

### Roger Fielding, Ph.D. Professor of Medicine

Researcher studying the underlying mechanisms contributing to the age-associated decline in skeletal muscle mass

Published over 200 per-reviewed papers and 8,000 citations

Conducted numerous studies examining the roll of skeletal muscle power on physical performance in older adults

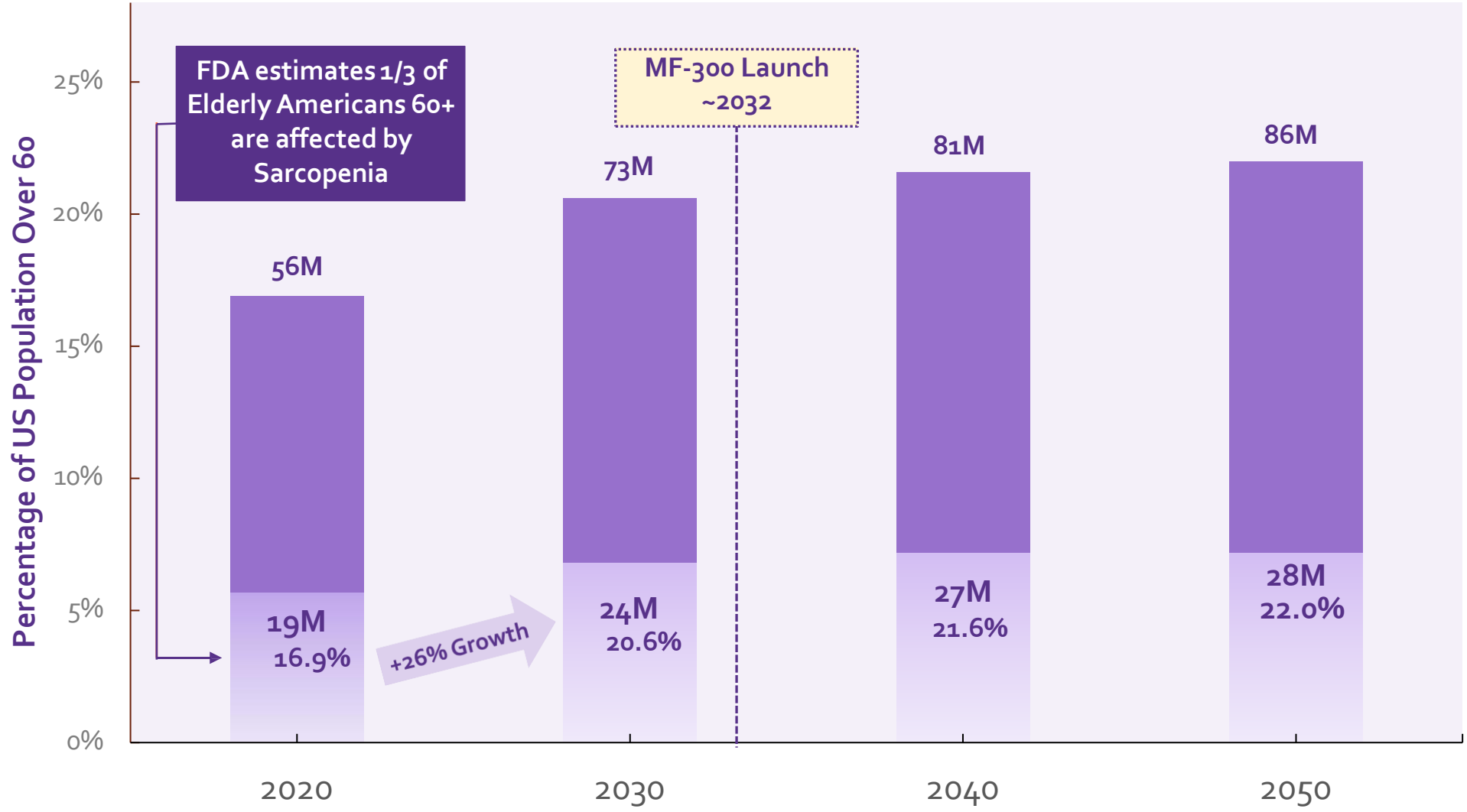
# Large and Growing Unmet Medical Need
# No FDA Approved Therapy

## Current U.S. Healthcare Sarcopenia Spending Estimated >$40 Billion Annually

**Dependence**
"At-risk" of losing independence

**Falls**
Increased Morbidity & Mortality

**Mortality**
Increased risk of death




Source: Burns ER, J. Safety Res. 2016, U.S. Population est. 331M

# Sarcopenia Root Cause: Diminished Muscle Quality

## Sarcopenia:

- **Severe loss of muscle strength** and mass with aging
- **Strength declines faster than muscle mass**[1] due to **Diminished muscle quality**[2,4]
  - Existing muscle is weaker, contracts slower
  - Disproportionate loss of fast twitch muscle force
  - Progressive denervation of muscle
  - Reduced regenerative potential of muscle stem cells

**Strength decline outpaces reductions in muscle mass with aging**[1]

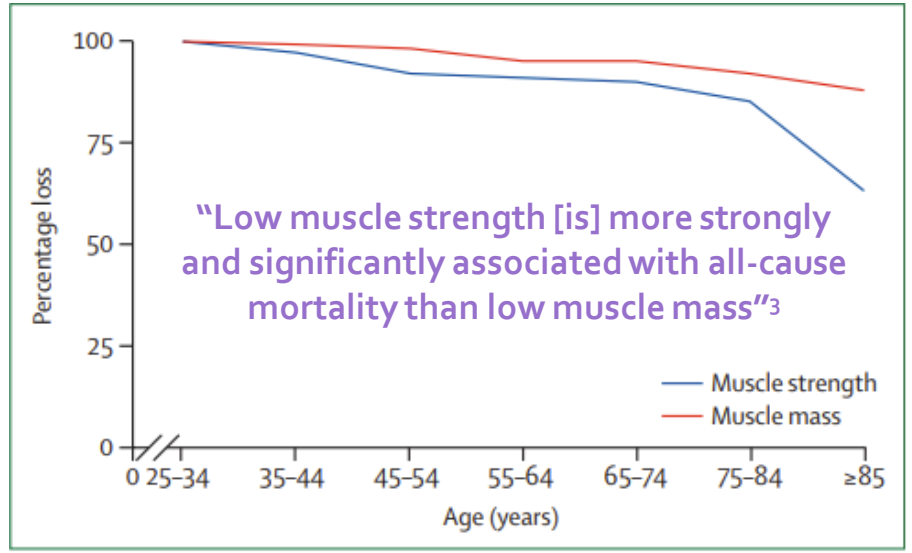



*Figure 1:* **Percentage loss of muscle mass and muscle strength with age in men**

**"Maintaining or gaining muscle mass does not prevent aging-associated declines in muscle strength"**[5]

[1] Cruz-Jentoft and Sayer, *Lancet*, 2019
[2] Jubrias and Conley, *Fun. Neurobio. of Aging*, 2001
[3] Li et al., *Med Sci Sports & Exercise*, 2017
[4] Mohien et al., *eLife*, 2019
[5] Goodpaster et al., *J Gerontology*, 2006

# 15-PGDH, a Gerotherapeutic Target, Reduces PGE2 Levels, is Upregulated in Aged Muscle

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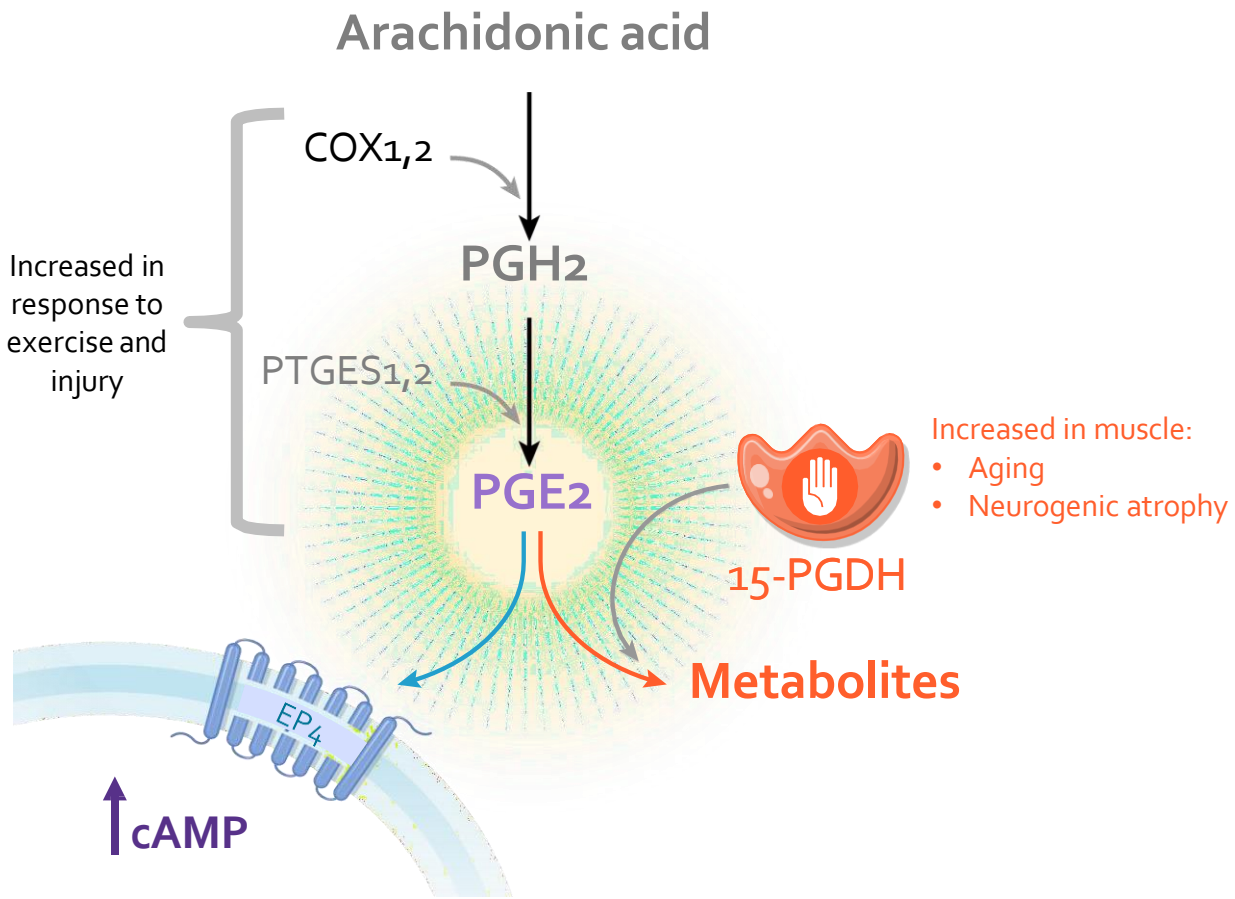
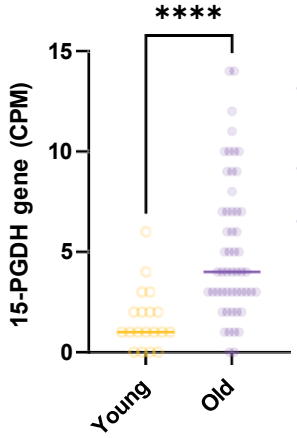
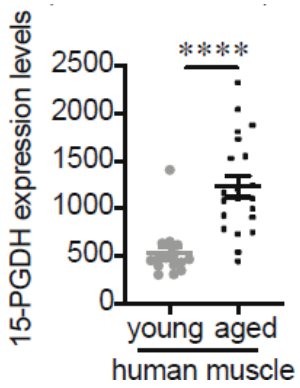
## 15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2




## 15-PGDH gene expression Elevated in aged human muscle[3,4]

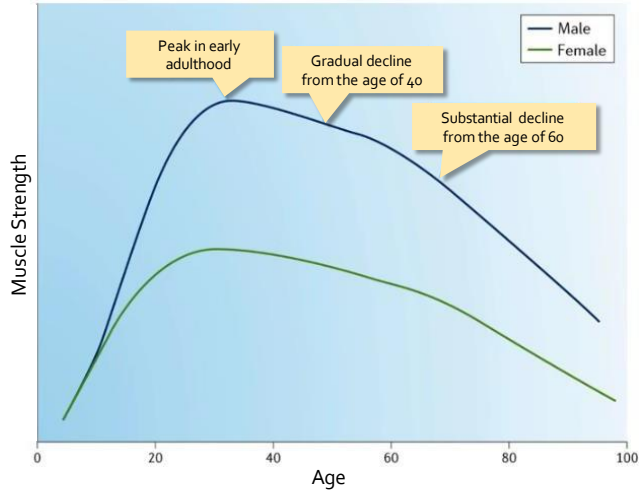



- Vastus lateralis (women and men)
- Young, N = 19 (**25±3 y.o.**)
- Older, N = 29 (**78±6 y.o.**)




- Vastus lateralis, RNA-seq (men)
- Young, N = 19 (**avg. age 20 y.o.**)
- Older, N = 29 (**avg. age 57 y.o.**)

### Grip strength, a predictor of sarcopenia risk, declines with age[5]




[3] GEO167186, [4] Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), [5] Dennison et al., *Nat Rev Rheum* 2017

# MF-300: Epirium's Therapeutic Strategy to Increase PGE2 Levels in Aged Muscle

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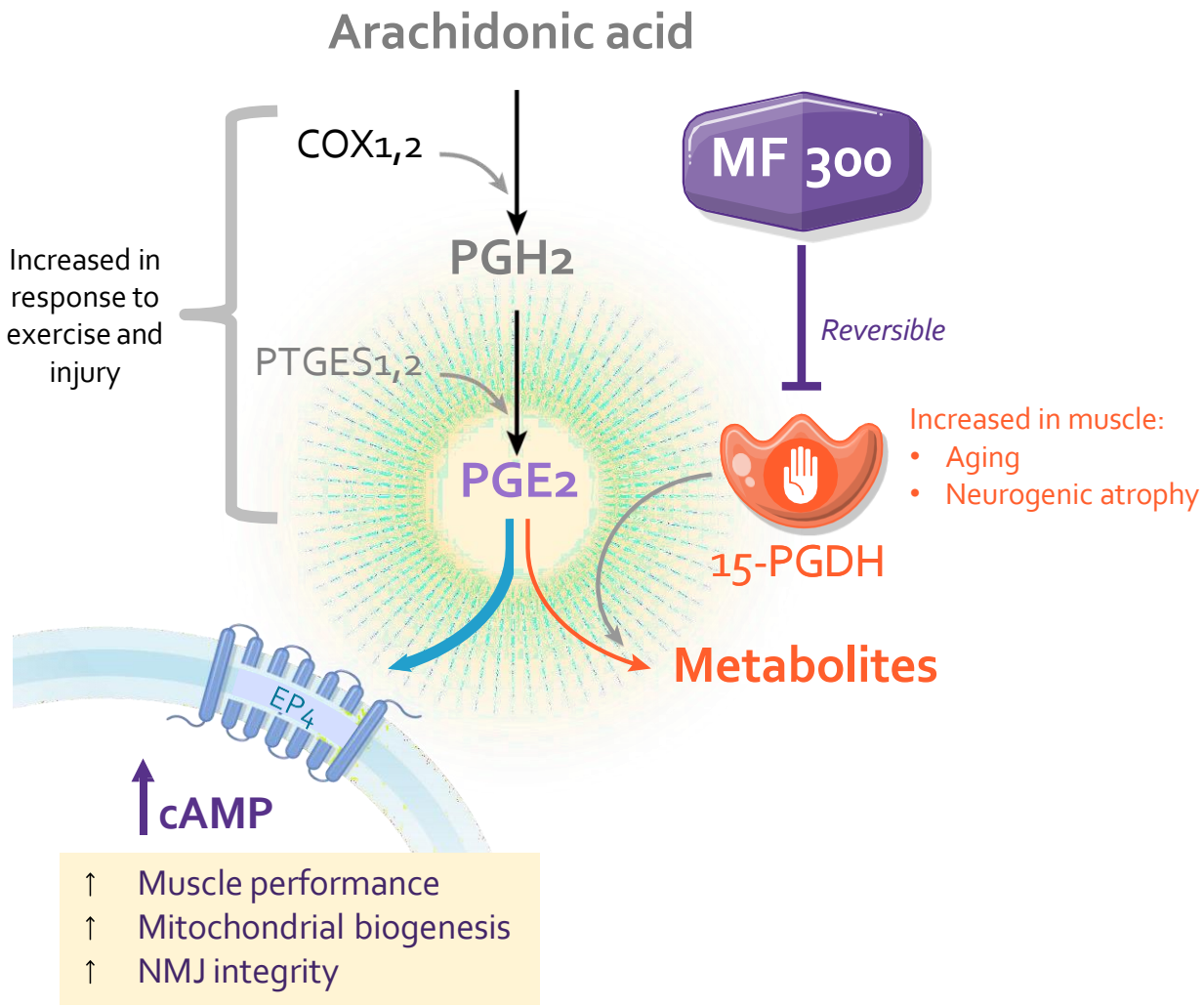
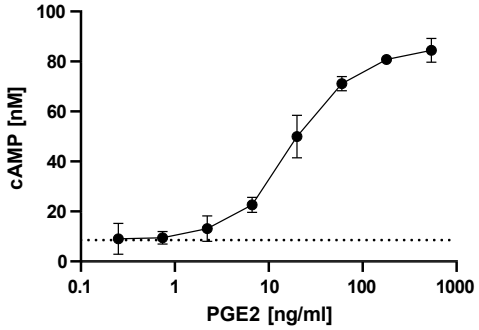
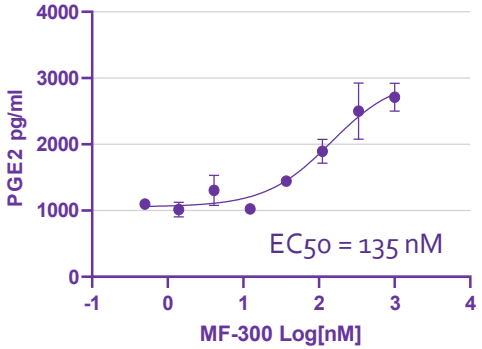
## MF-300
## Inhibits 15-PGDH to increase levels of PGE2




**PGE2 increases cAMP in primary human myocytes**




**MF-300 increases PGE2 in cell-based assay**



# MF-300 Increases Muscle Force with Correlated Reduction in PD Biomarker

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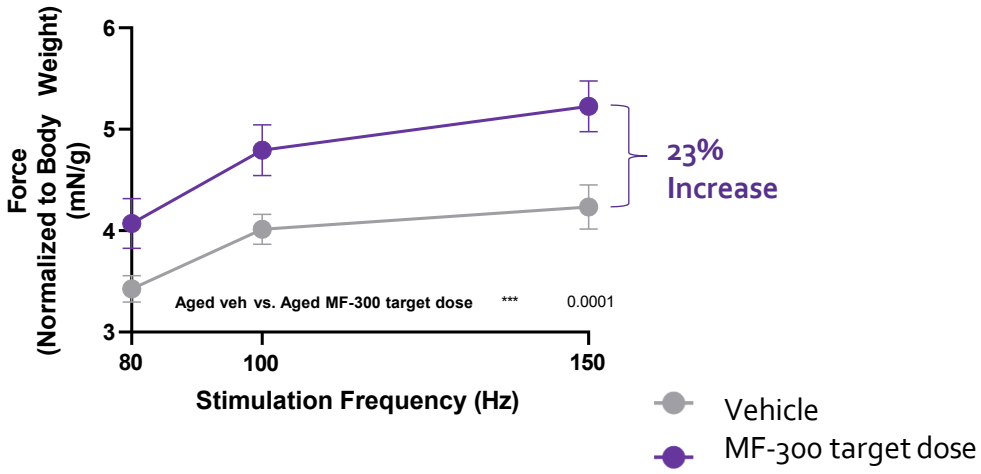
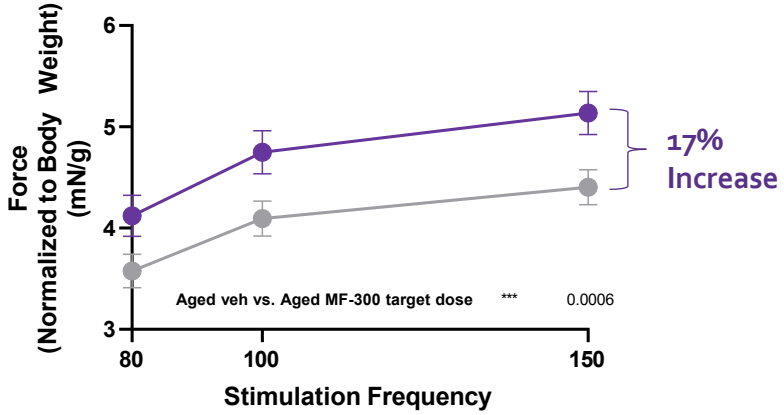
## MF-300
## Increased muscle force in aged mice

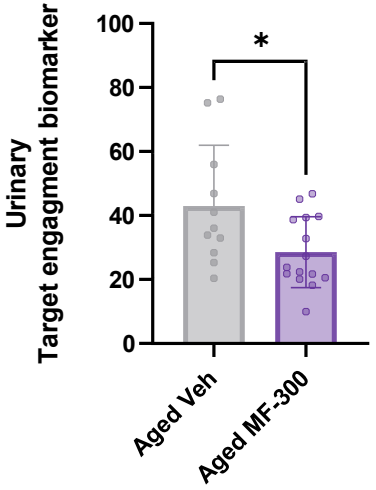
### Study 1

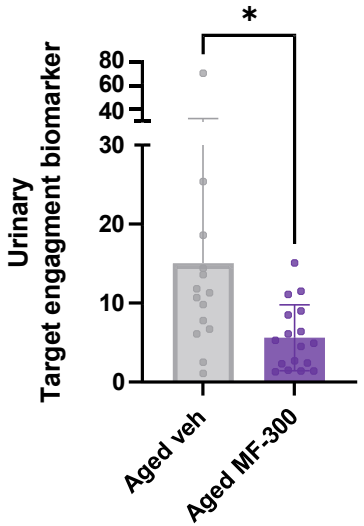



### Study 2




## MF-300
## Reduced urinary metabolite of PGE2



## Clinical Update

- Phase 1 Overview
- Phase 2 Planning: Design & Endpoints

# Phase 1 Overview

**Objectives:** **Assess the safety and tolerability of MF-300 following single ascending doses (SAD) and multiple ascending doses (MAD) along with:**

- MF-300 Pharmacokinetics (PK) & Pharmacodynamics (PD), including target engagement (TE) biomarkers
- Potential for food effect on the PK of MF-300 following a single oral dose
- Characterize the PK/PD, PK/safety relationships, allowing for Ph2 dose selection

**Population:** **Adult healthy volunteers ≥ 18 - < 65 years of age & Healthy Elderly Cohort ~65-75 years of age**

## Part 1a SAD

- N=8 per cohort (2 pbo, 6 MF-300)
- Broad range of doses
- Large safety margin
- Allows for flexible dosing
- Elderly cohort dose selection

**Single Ascending Dose**
**5 dose adult cohorts, 1 elderly cohort**

## Part 1b Food Effect

- N=12 (all MF-300)
- MF-300 administered in the fed or fasted state

**Food Effect**
**2 sequence 2 period cross-over**

## Part 2 MAD

- N=10 per cohort (2 pbo, 8 MF-300)
- Daily dosing for 5 days to achieve steady state PK

**Multiple Ascending Dose**
**3 dose adult cohorts & 1 Elderly follow-on cohort**

# Phase 1 Expected Results: Conclusions & Phase 2 Dose Selection

## Safety and Tolerability

- Single and multiple doses of MF-300 are well-tolerated, safe dose range determined
  - AEs, Physical exams, Vitals, ECGs, & Labs

## Pharmacokinetics

- MF-300 exhibits accept PK over the dose range tested
- Food intake affect MF-300 absorption & bioavailability
- PK profile and key PK parameters were well-characterized
  - Cmax, Tmax, AUC, T ½

## Pharmacodynamics

- Proof of concept: Initial biomarker responses suggest target engagement at certain doses
- Dose response, exposure-response (E-R) relationships characterized to allow Ph2 dose selection

## Implications for Phase 2

**Data Supporting Phase 2 Dose Selection:**

- Identified therapeutic window informing Phase 2 dose selection based on safety and PK findings, supplemented by Efficacy-Response (E-R) relationships:
  - Strong E–R relationship is observed, positioned to determine optimal dose / exposure target for Phase 2 dose selection

# Current Phase 2 Design: 24-week Duration w/ 12-week Interim Analysis

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## Overview

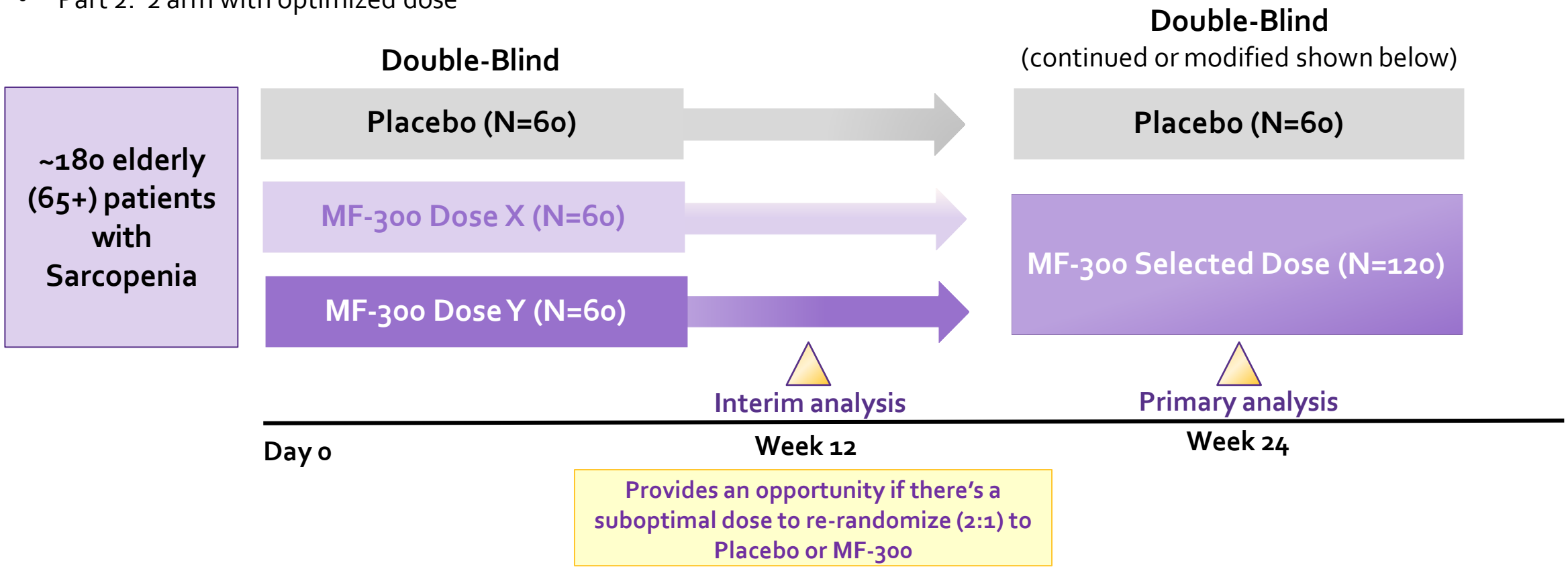
- 24 week randomized, double-blind, placebo-controlled, adaptive design
- Part 1: 3 arm, dose-finding (60/arm)
- Part 2: 2 arm with optimized dose

## Interim Analysis

Analysis 20/arm at Week-12

## Primary Analysis

Primary Endpoint: Functional Benefit & Secondary Endpoints



# Phase 2 Planning: Entry Criteria & Indication Relevant Endpoints

## Entry Criteria

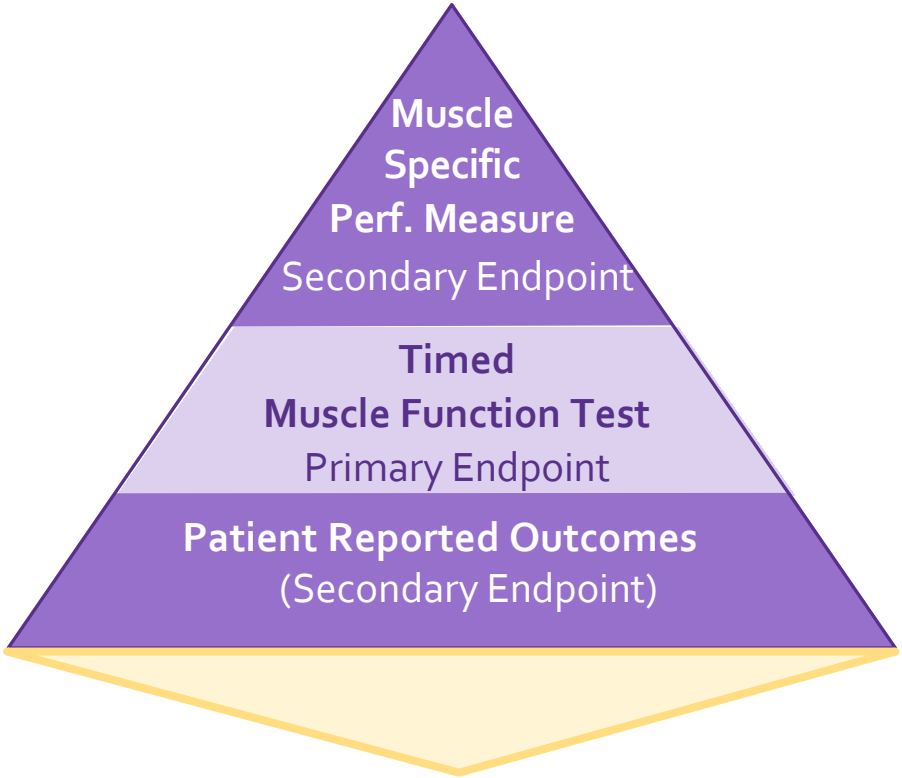
**Elderly (≥65 yo)[1] men and women with sarcopenia according to SDOC definition[2]**

- Low grip strength (<35.5 kg for men, <20 kg for women) &
- Slowness (walking speed <0.8 m/s)
- SPPB* Score 4 – 8

*SPPB = Short Physical Performance Battery (12 pt Scale higher better)


1. Reginster JY, et al. Aging Clin Exp Res. 2021;33:3-17.
2. Bhasin S, et al. J Gerontol A Biol Sci Med Sci. 2023;78:S86–S93.


## Sarcopenia Indication Criteria




**Meaningful Patient Benefit**

## Endpoints

**Primary Endpoint Measure**:
CFB vs. PBO

**Key secondary endpoints**:
CFB vs. PBO in

- Muscle specific measures
- Timed walk test
- SPPB*
- PROs
  - ➢ PROMIS – Physical
  - ➢ SarQol

# Series B Funded Milestones: MF-300 Phase 2 Data Readount & IND Ready IND

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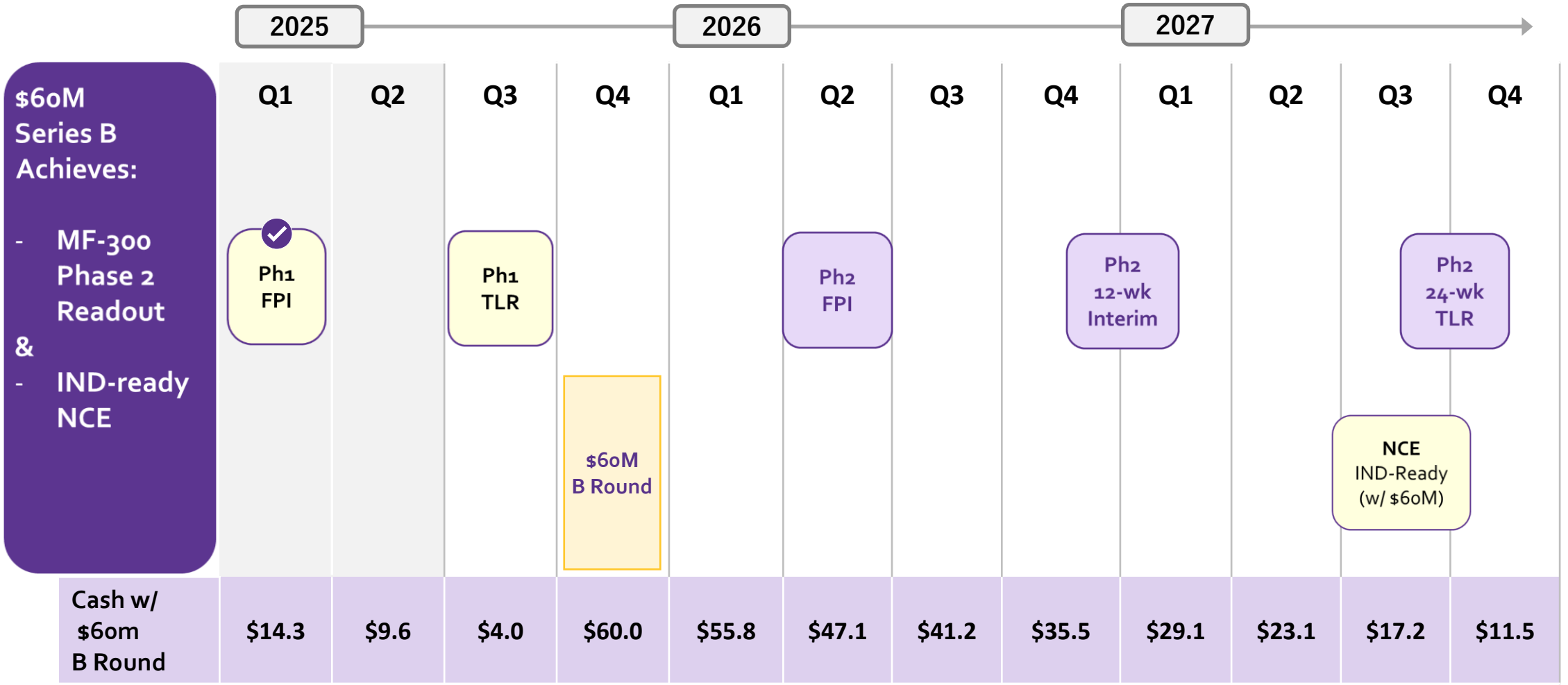

# MF-300 Value Creating Milestones over next 6 months

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## Phase 1 SAD/MAD Initial Topline Results – Sep '25

- Results include PK/PD and Target Engagement (TE) Biomarkers

## Phase 1 Presentation Targeted for GSA Meeting – Nov '25

- Key KOL outreach opportunity

## FDA Input on Phase 2 Plans – Jan '26

- Leveraging Sarcopenia & Regulatory Advisors, PRO & Muscle Function Study

## ✓ MF-300 + MSTNi Muscle Mass & Force Efficacy in Δ7 SMA Model

- Broadens Indication Opportunities: Sarcopenic Obesity, Sarcopenia & Rare Disease

## Results from Colitis Prevention Study (DSS) w/ NCE MF-1305

- Leverages interest in IBD, sets stage for value-creating treatment

# Positioned to Capitalize on "Oral Small Molecule Pipeline in a Mechanism"

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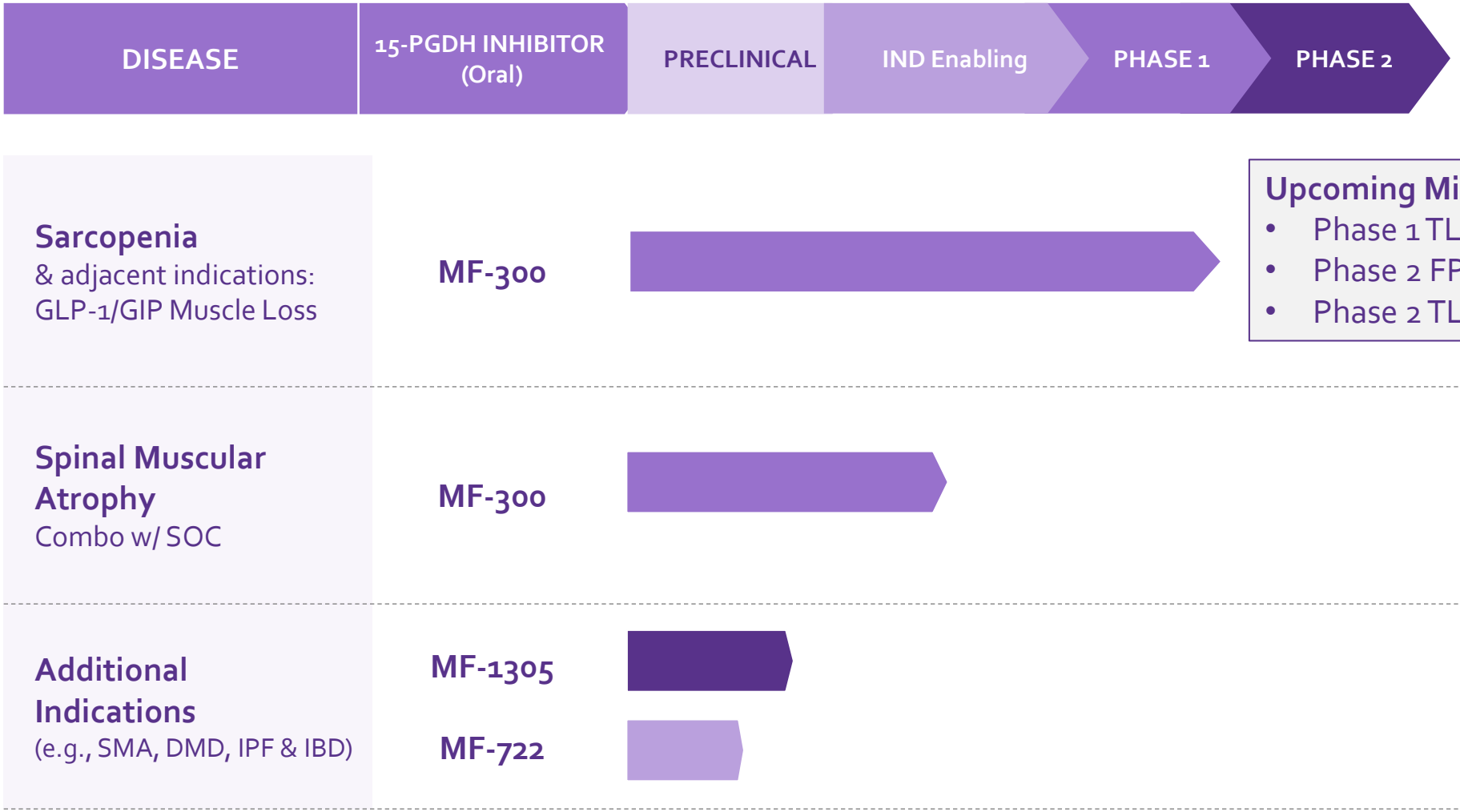

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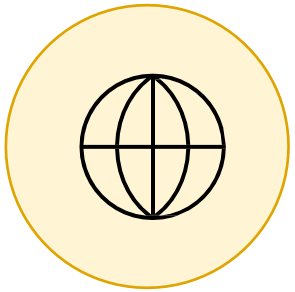
# Thank you!



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info@epirium.com

## Spinal Muscular Atrophy Recent Data Review:

- Prior MF-300 and m-Apitegromab monotherapy efficacy in Delta7 SMA Mouse Study
- **Recent (June '25) combo data MF-300 + MNSTi available under CDA**

# MF-300 Attractive Profile in Translational SMA Model in Mice

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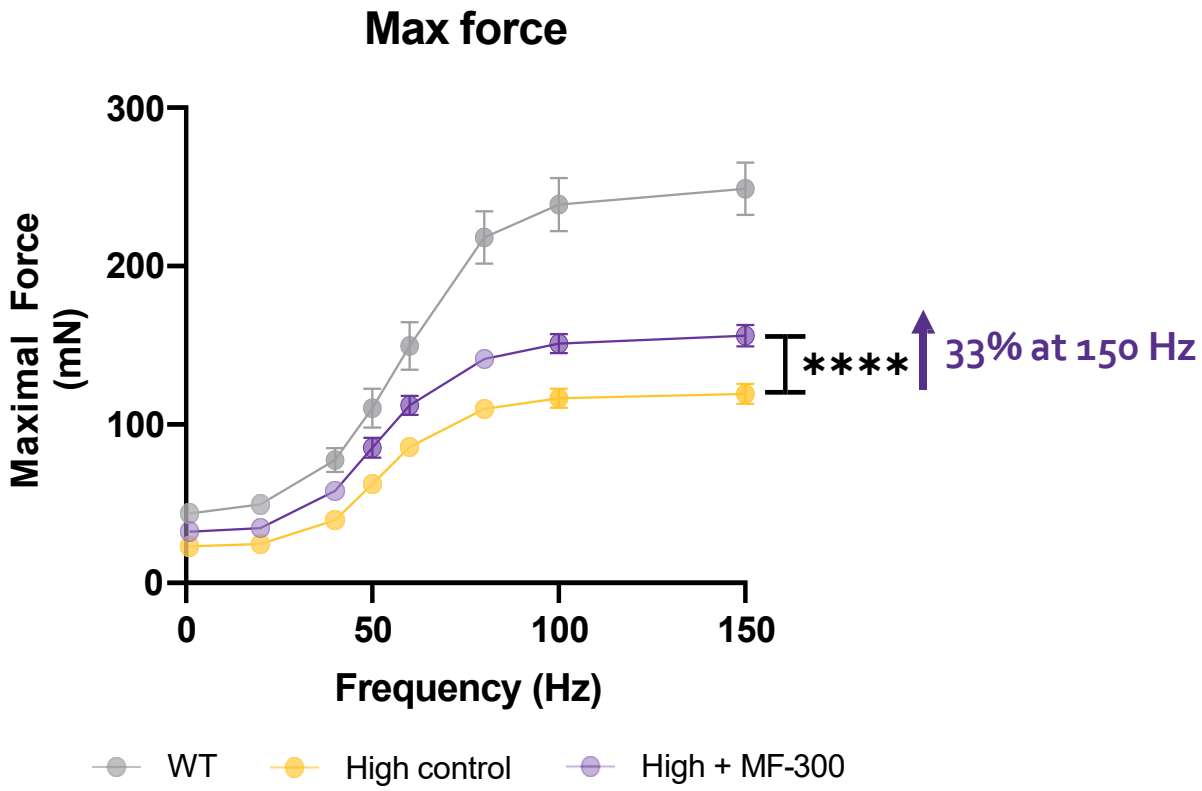
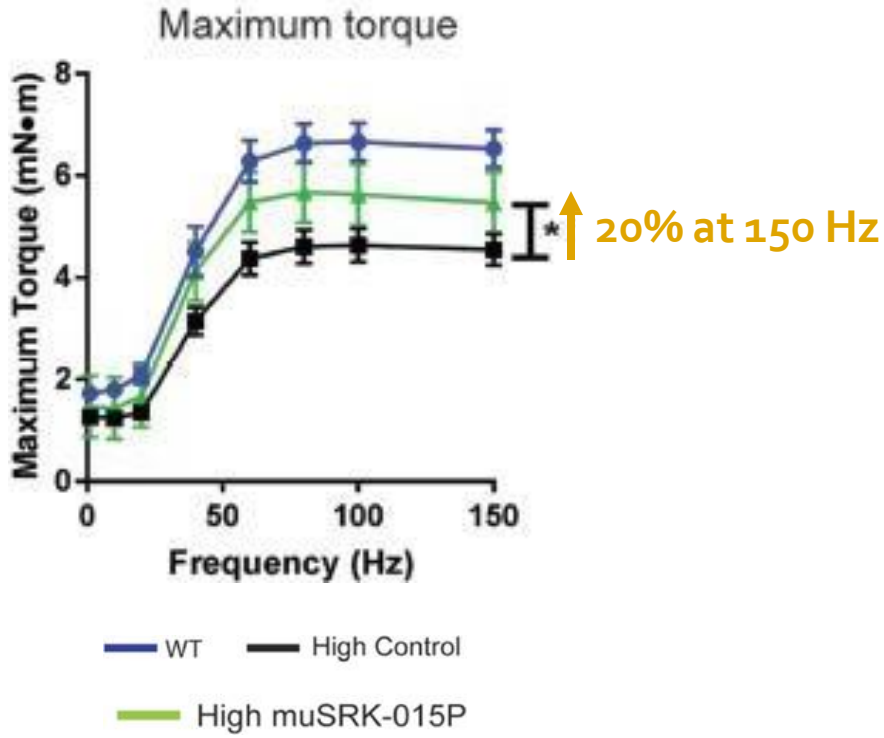
## MF-300 in SMNΔ7 High/High




## mSRK-015P in mouse Δ7 High/High




Force = Torque

MYOLOGICA

# Scholar Rock's Preclinical and Clinical Data Set Precedent for Translation of Efficacy

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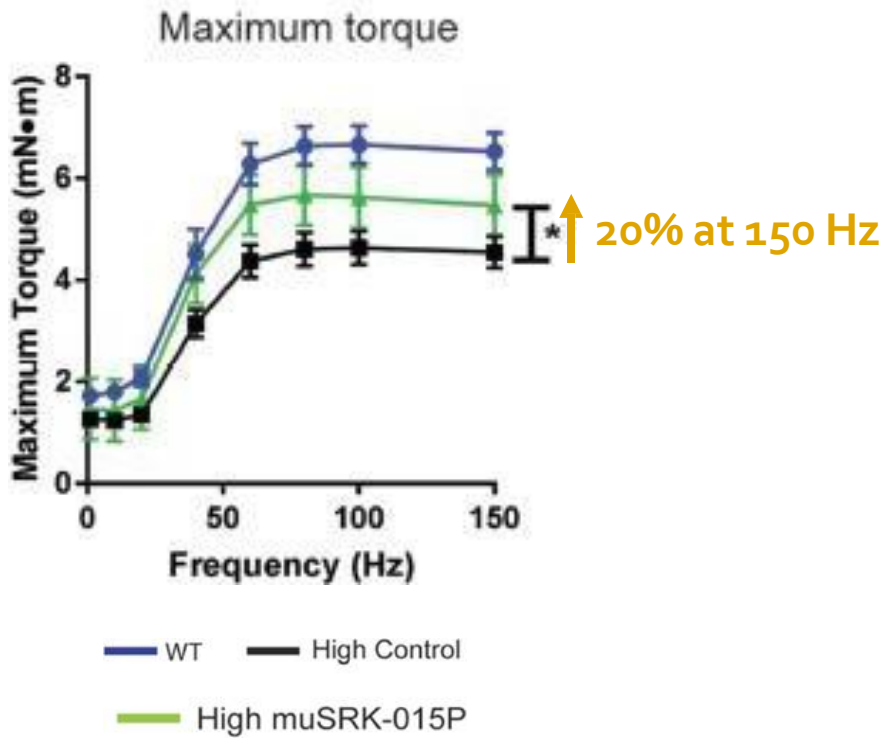
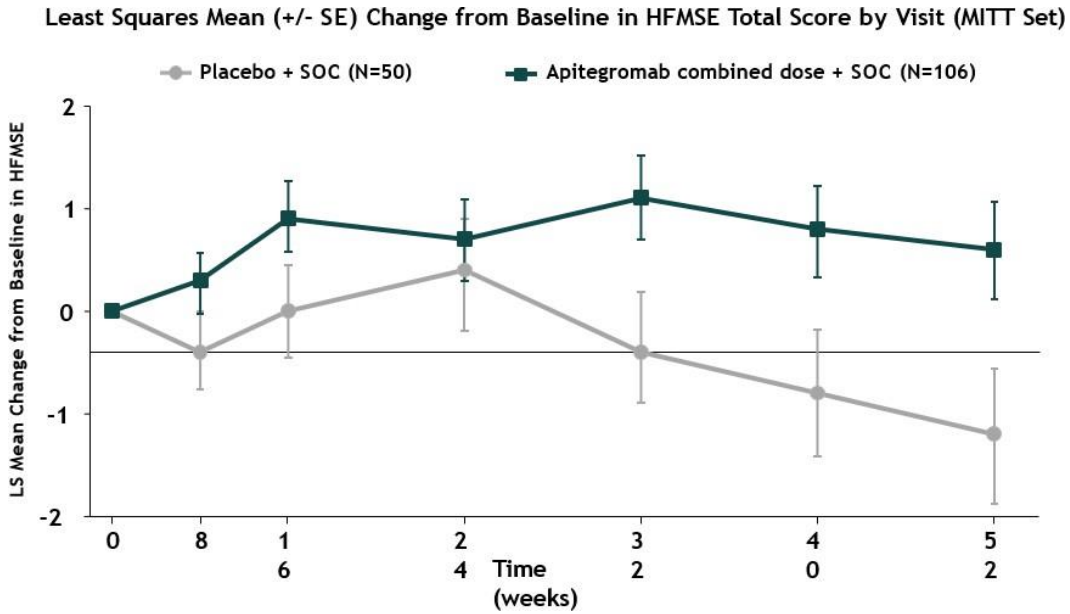
## Demonstrates that a 20% increase in isometric plantar flexor force in mice translates to clinical benefit

### mSRK-015P in mouse Δ7 High/High




### Apitegromab in SMA + SOC (Ph 3 SAPPHIRE)




Change from Baseline in HFMSE Total Score

| | Analysis | n | Results (vs Placebo, n=50) | Unadjusted *P*-value | |
|---|---|---|---|---|---|
| Primary Analysis | Apitegromab 10+20 mg/kg combined | 106 | 1.8 | 0.0192* | ✓ Achieved Statistical Significance |
| | Apitegromab 20 mg/kg | 53 | 1.4 | 0.1149* | |
| | Apitegromab 10 mg/kg | 53 | 2.2 | 0.0121** | |

ScholarRock

Long et al., *Hum Mol Gen*, 2016