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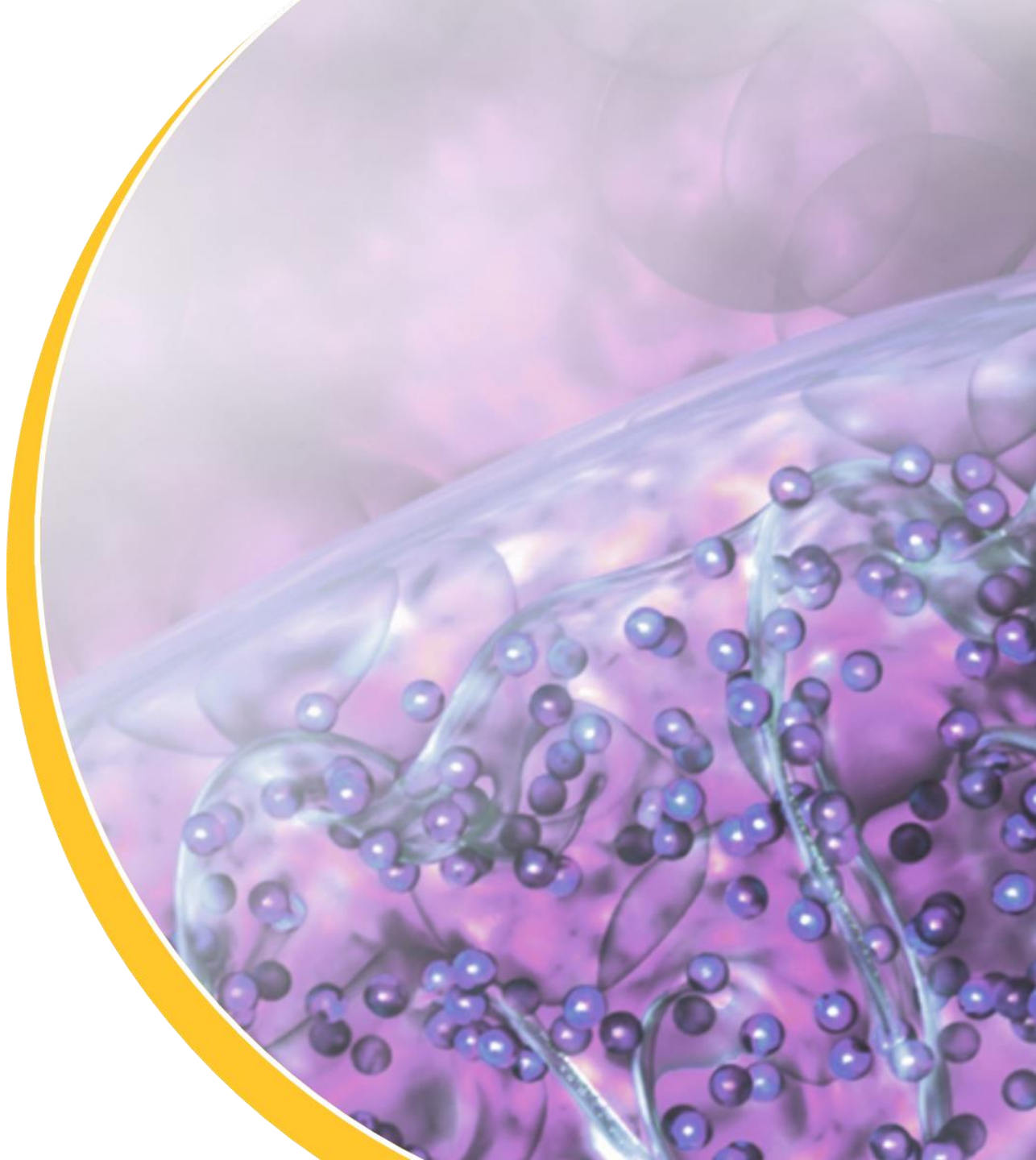
Novel Platform: Pipeline in a Mechanism, Oral Treatments for Neuromuscular Diseases

- **MF-300 "First-in-Class" Oral Therapy for Sarcopenia**
- **Additional Rare Disease Opportunities**:
  - Neuromuscular: Spinal Muscular Atrophy (SMA)
  - Fibrotic: Idiopathic Pulmonary Fibrosis (IPF)



Experienced Team with a Demonstrated Track Record of Success

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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

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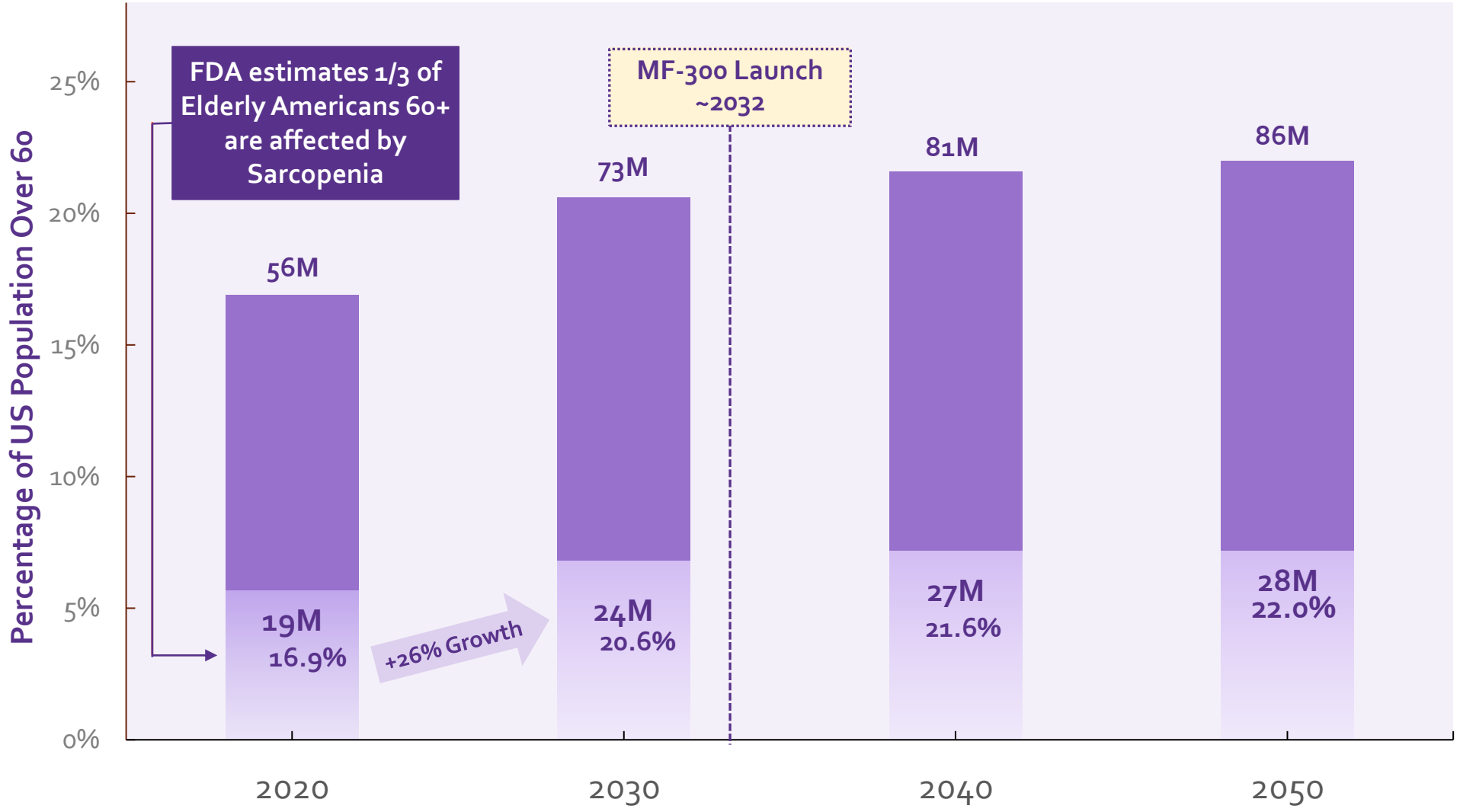
Current U.S. Healthcare Sarcopenia Spending Estimated >$40 Billion Annually

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

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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]

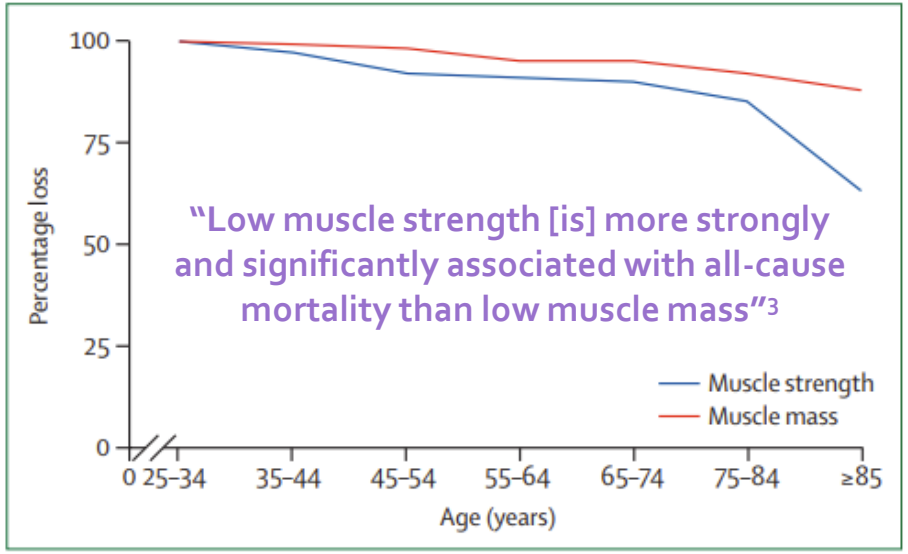

Figure 1: **Percentage loss of muscle mass and muscle strength with age in men**

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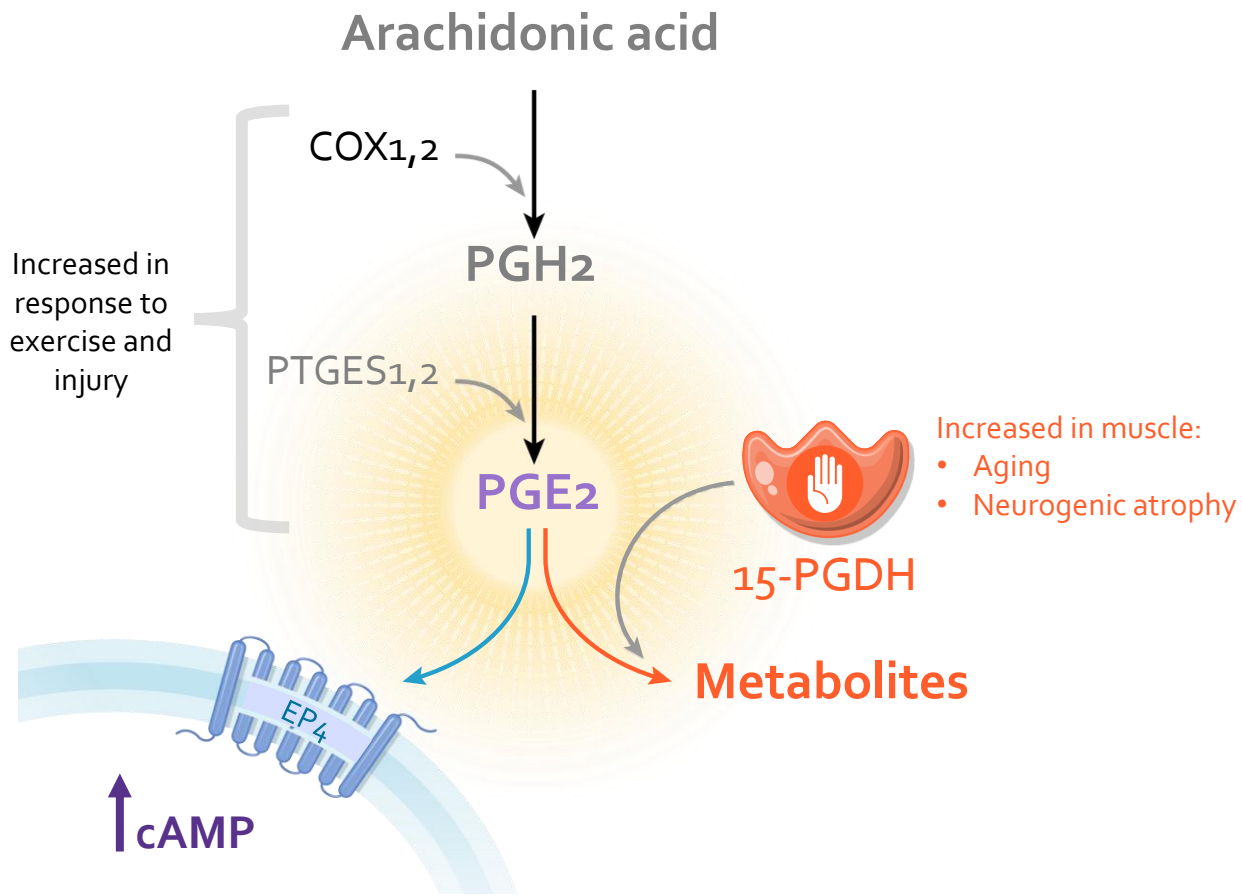
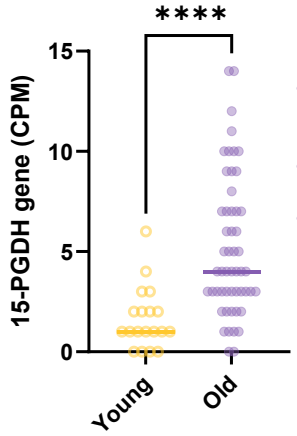
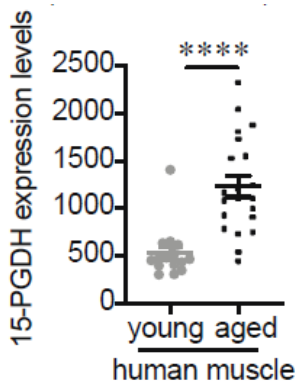
15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2



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

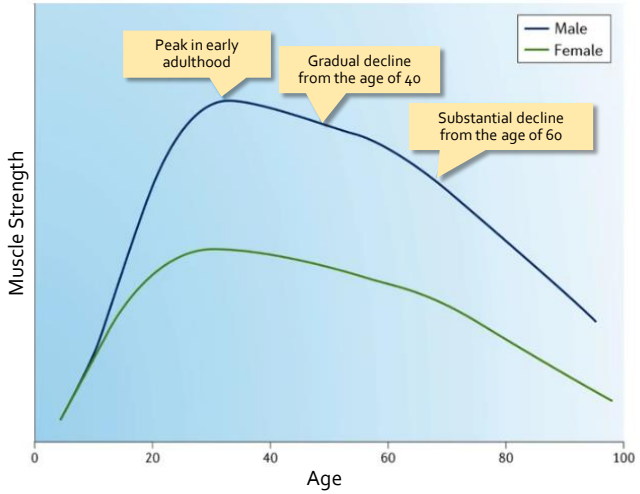


- Vastus lateralis (women and men)
- Young, N = 19 (**25±3 y.o.**)
- Older, N = 29 (**78±6 y.o.**)



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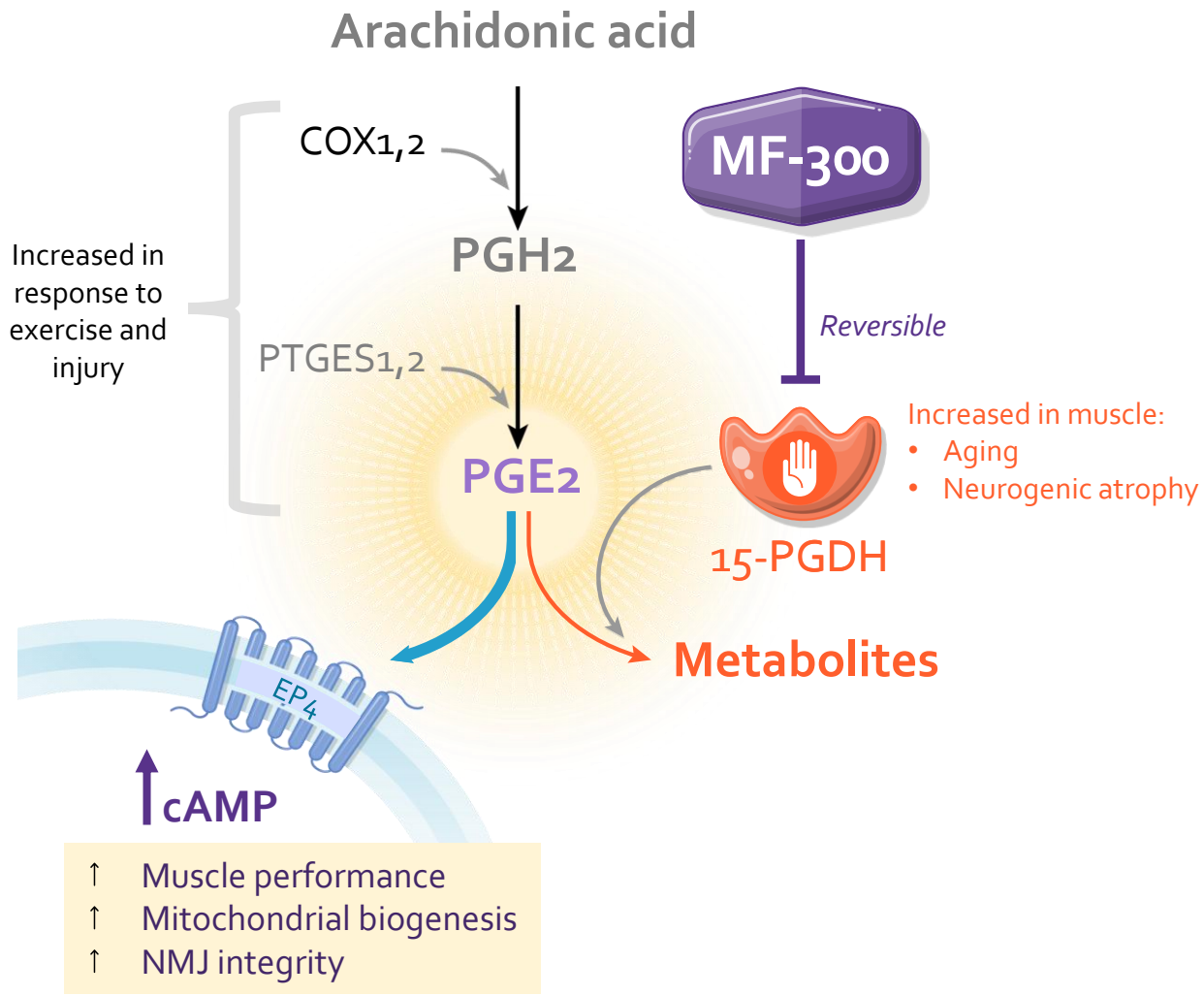
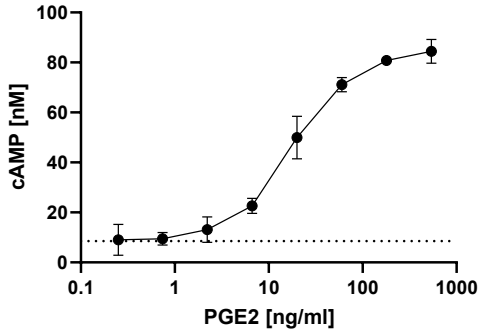
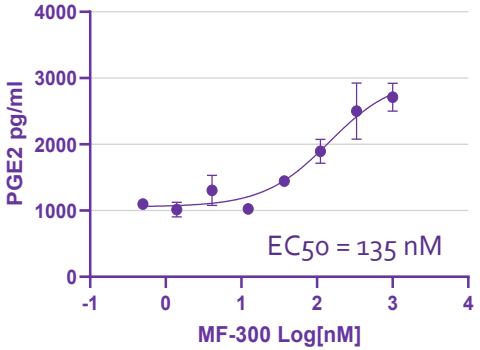
MF-300
Inhibits 15-PGDH to increase levels of PGE2



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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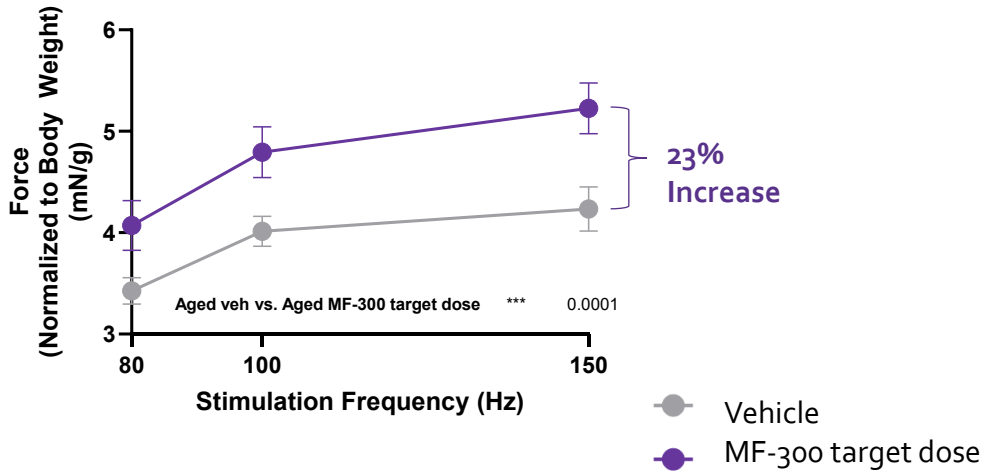
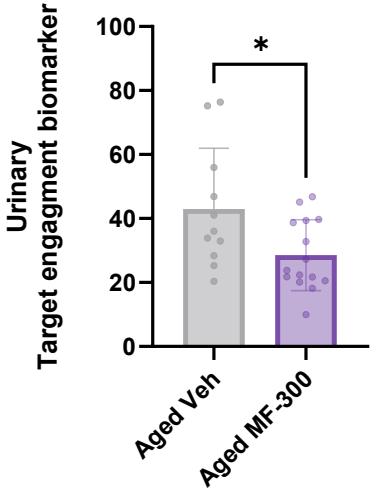
MF-300 Increased muscle force in aged mice

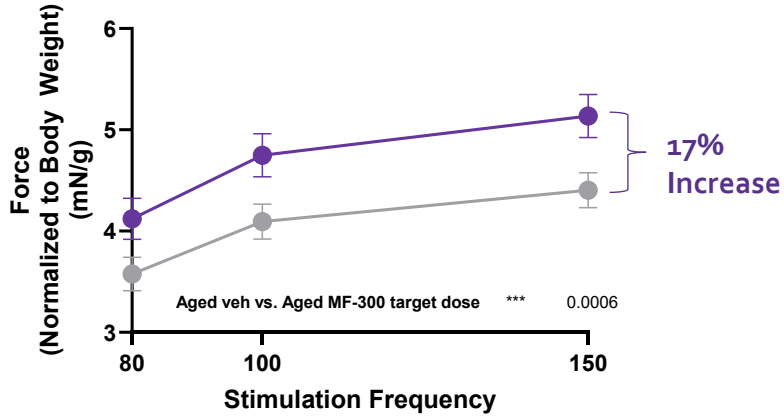
MF-300 Reduced urinary metabolite of PGE2

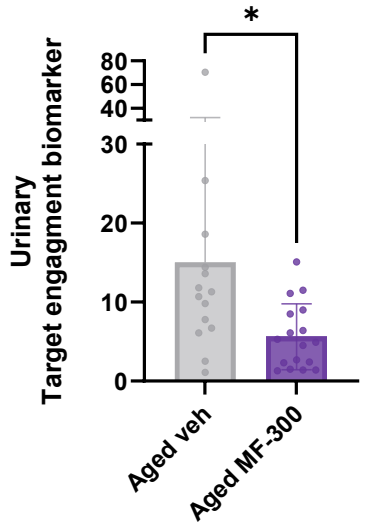
Study 1





Study 2





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 cohort

Phase 1 Expected Results: Conclusions & Phase 2 Dose Selection

Safety and Tolerability

- Single and multiple doses of MF-300 are well-tolerated at the tested doses with a maximum tolerated dose determined or a safe dose range determined
  - AEs, Physical exams, Vitals, ECGs, & Labs

Pharmacokinetics

- MF-300 exhibits linear or non-linear PK over the dose range tested
- Food intake did or did not affect MF-300 absorption and 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
- Micah will review Ph 1 proof concept target engagement biomarkers
  - Urine: PGE Metabolites
  - Plasma: PGE-2 and PGE Metabolites

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
  - Should resulting E–R be unclear, a broader dose range may be tested in Phase 2

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

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Overview

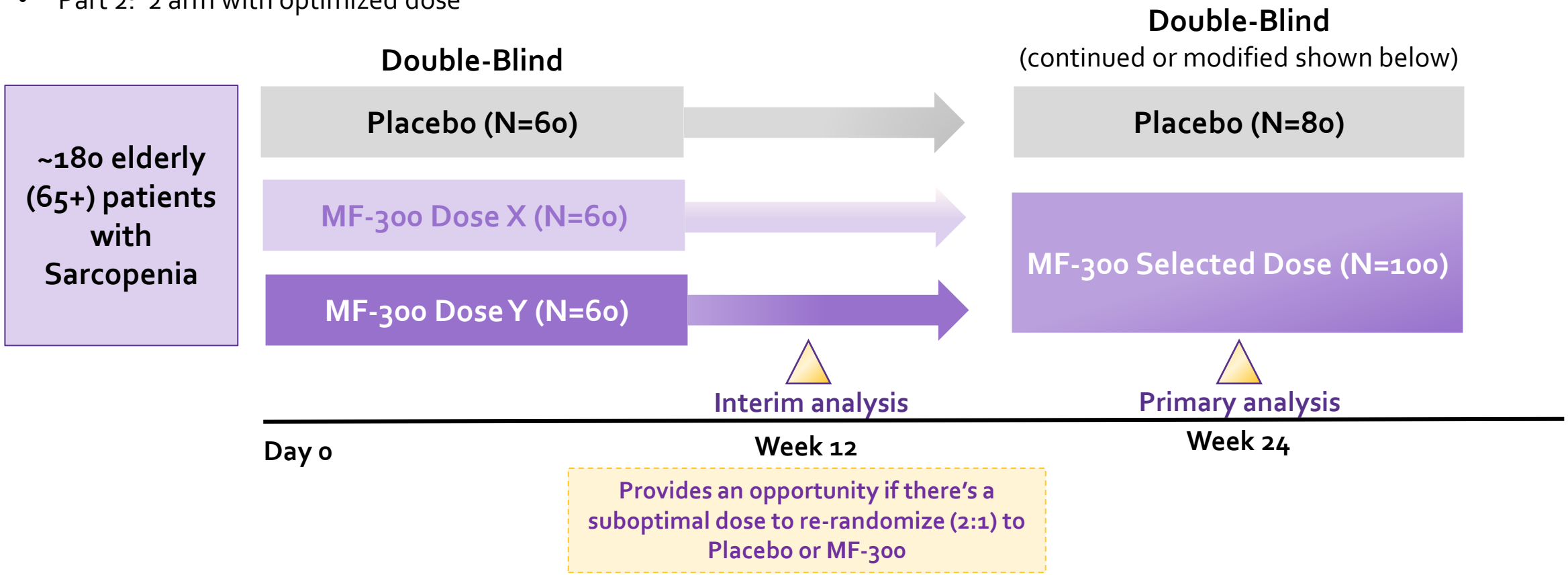
- 24 week randomized, double-blind, placebo-controlled, adaptive design
- Part 1: 3 arm, dose-finding (60/arm)
- Part 2: 2 arm with optimized dose

Interim Analysis

Analysis 20/arm at Week-12

Primary Analysis

Primary Endpoint: Functional Benefit & Secondary Endpoints



Phase 2 Planning, Assumptions & Endpoint Diligence during '25

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Entry Criteria

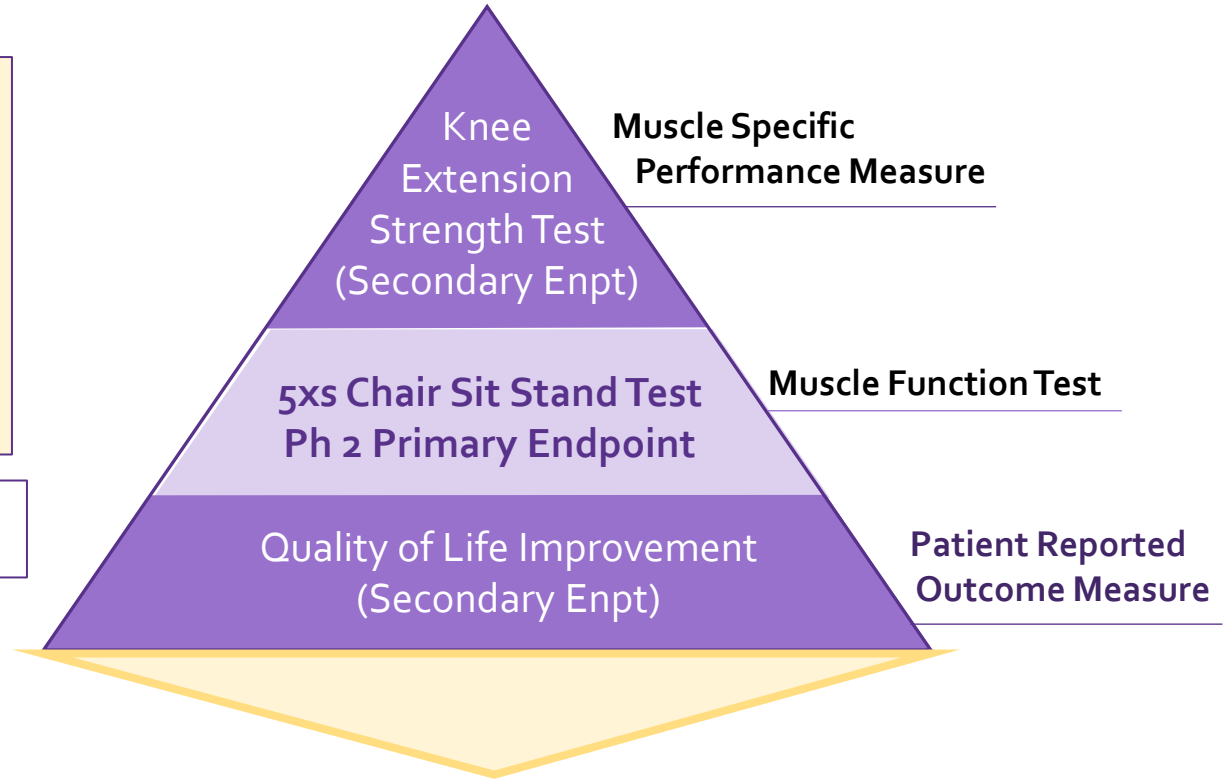
Elderly (≥65 yo)[1] men and women with sarcopenia according to SDOC definition[2]

- 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:
CFB vs. PBO
5xs Chair Stand Test (sec)

Key secondary endpoints:
CFB vs. PBO in

- Knee extension strength
- 4-meter gait speed test (sec)
- SPPB
- Hand grip strength (kg)
- PROs
  - ➢ PROMIS – Physical
  - ➢ SarQol

Phase 2 Study Key Milestones: Interim data Q4 '26 & Topline Readout H2 '27

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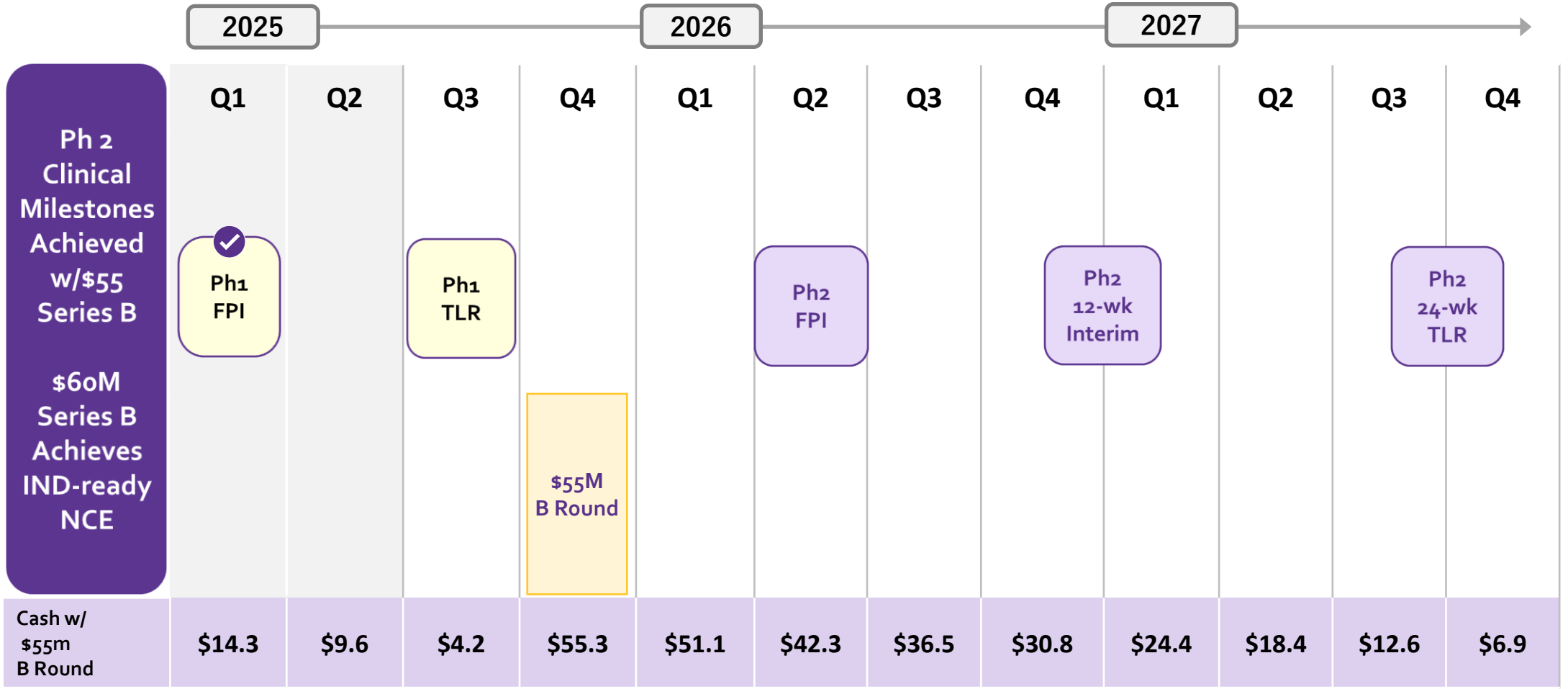

MF-300 Value Creating Milestones over next 6 months

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✓ **MF-300 + MSTNi Muscle Mass & Force Efficacy in D7 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

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 – Dec '25 / Jan '26

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

Positioned to Capitalize on "Pipeline in a Mechanism" Opportunity

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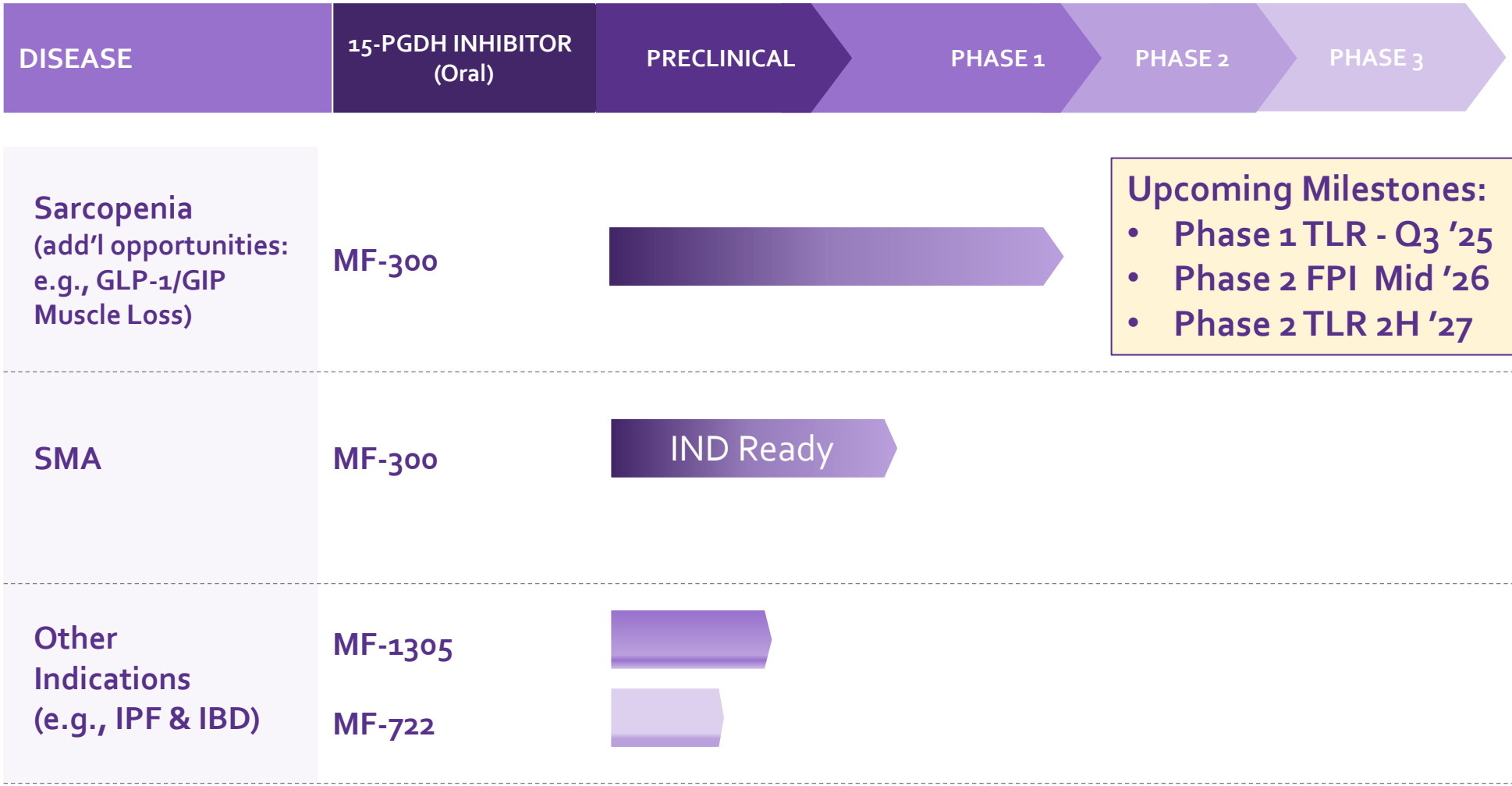

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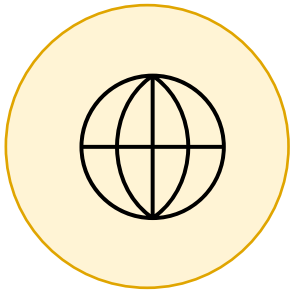
Thank you!



www.epirium.com

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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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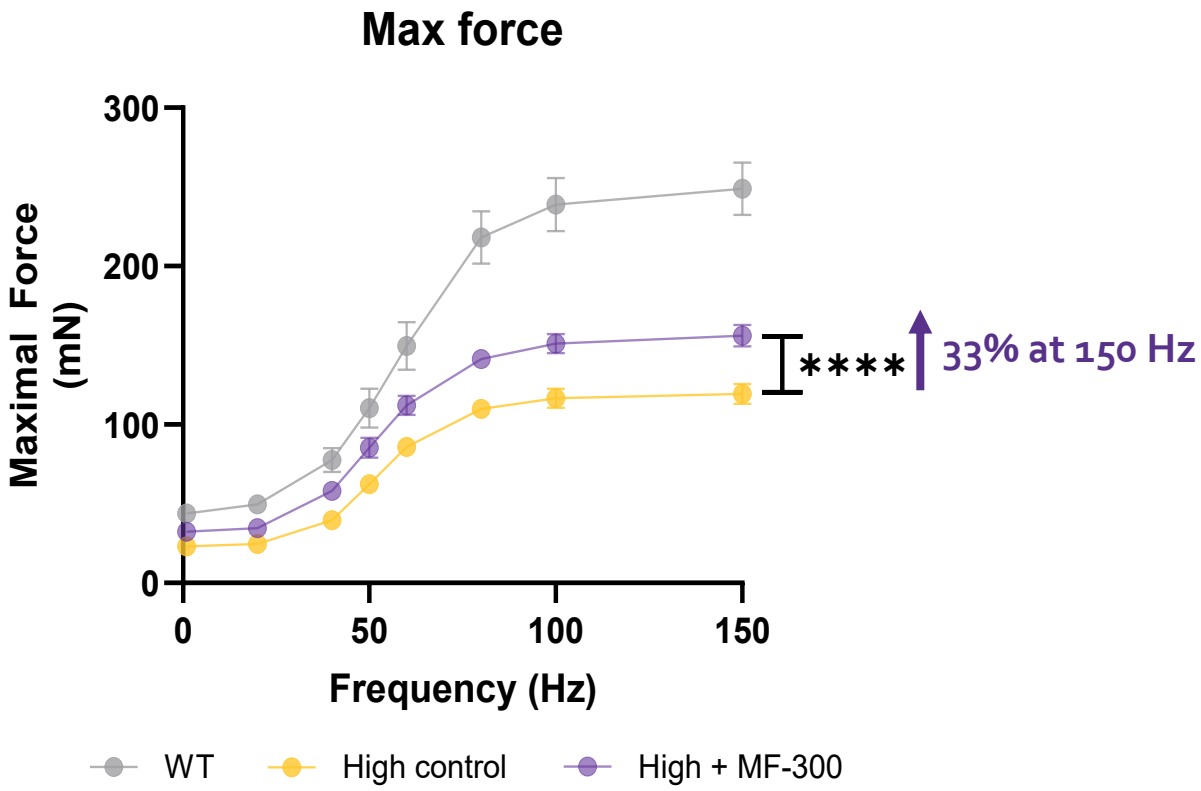
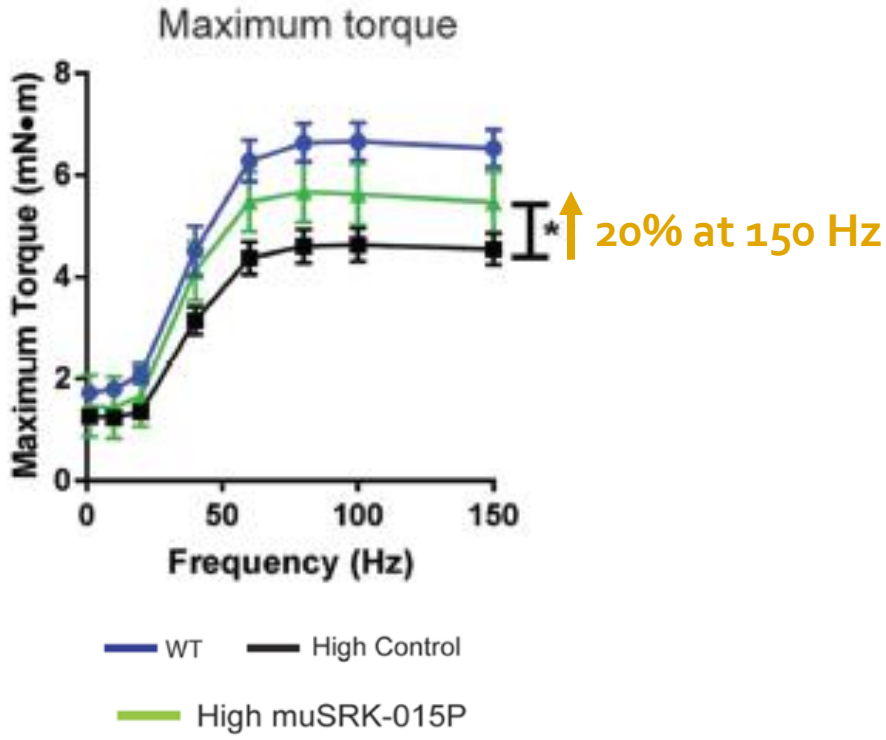
MF-300 in SMNΔ7 High/High



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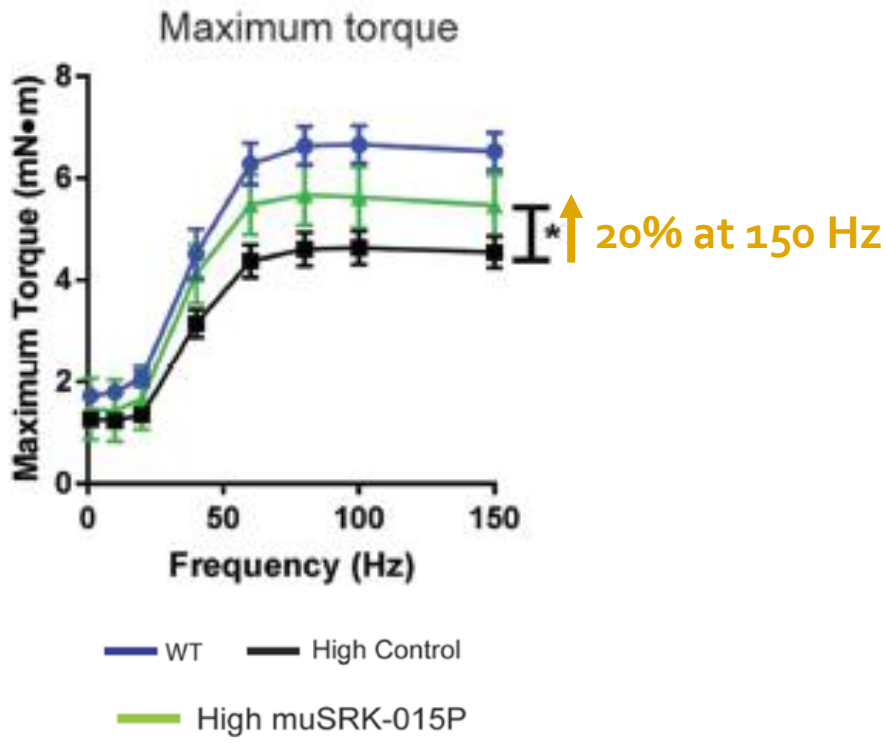
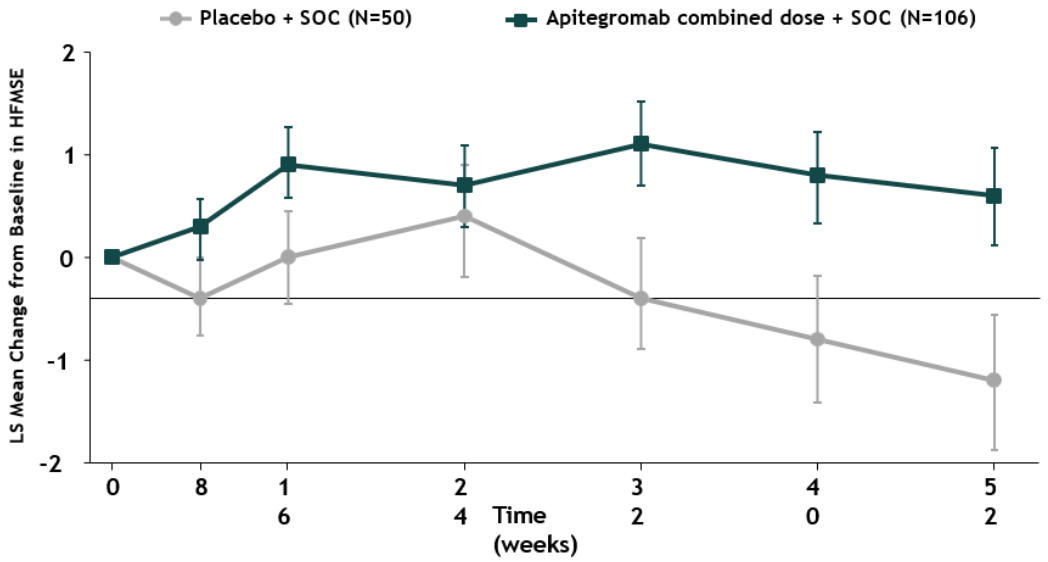
Demonstrates that a 20% increase in isometric plantar flexor force in mice translates to clinical benefit

mSRK-015P in mouse Δ7 High/High



Apitegromab in SMA + SOC (Ph 3 SAPPHIRE)

Least Squares Mean (+/- SE) Change from Baseline in HFMSE Total Score by Visit (MITT Set)



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