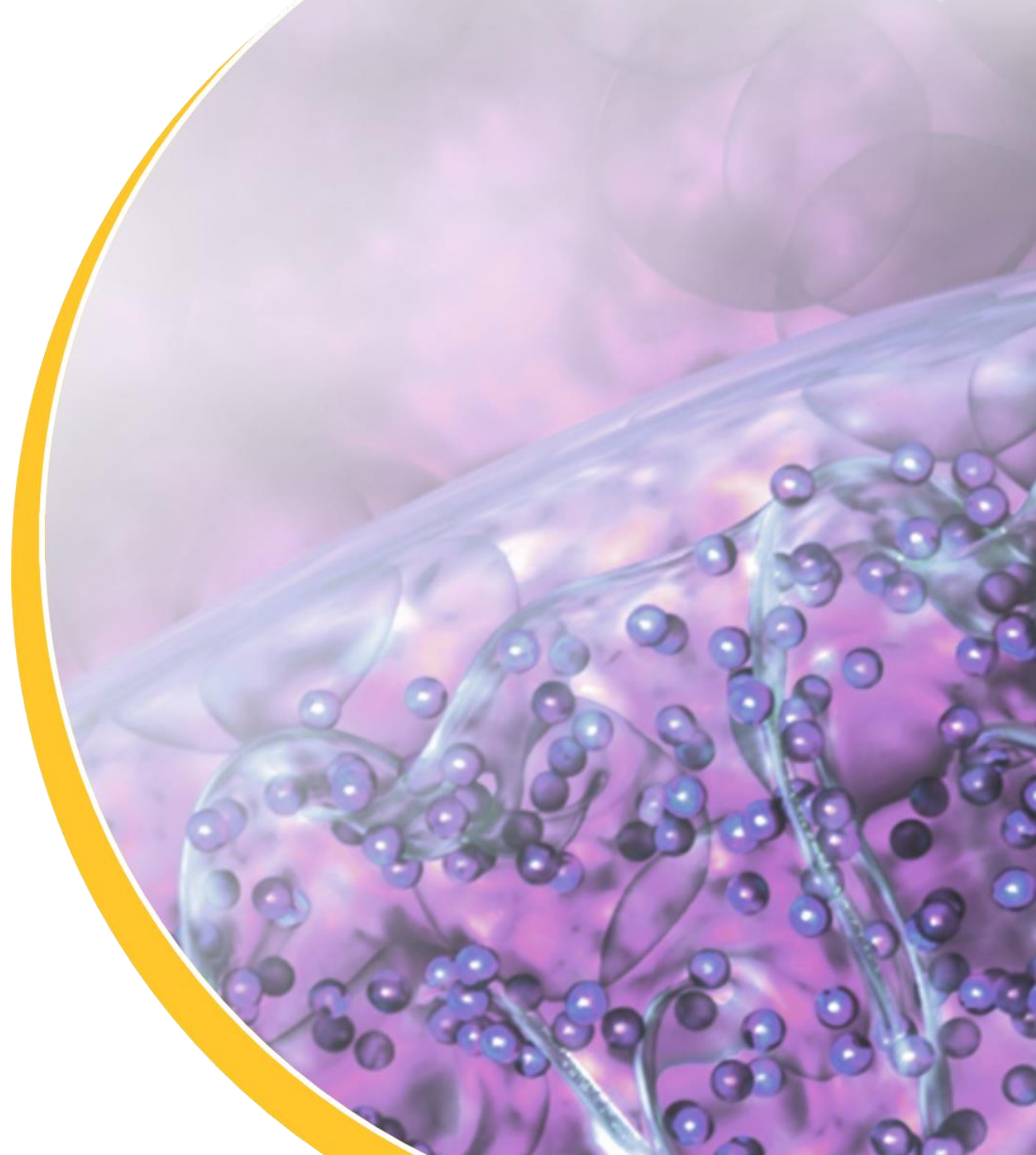




Novel Oral 15-PGDH Platform: Increasing Muscle Strength to Treat Sarcopenia and Neuromuscular Disease

- MF-300 “First-in-Class” Gerotherapeutic Oral Sarcopenia Therapy
- MF-300 + Myostatin Inhibitor Proof of Principal Efficacy in SMA SMN Δ 7
- Additional Opportunities: Sarcopenic Obesity, Rare Disease & IBD



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, Ph.D. Sr. Director, TS

Ph.D. in 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

Sarcopenia: Large and Growing Unmet Medical Need

No FDA Approved Therapy

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



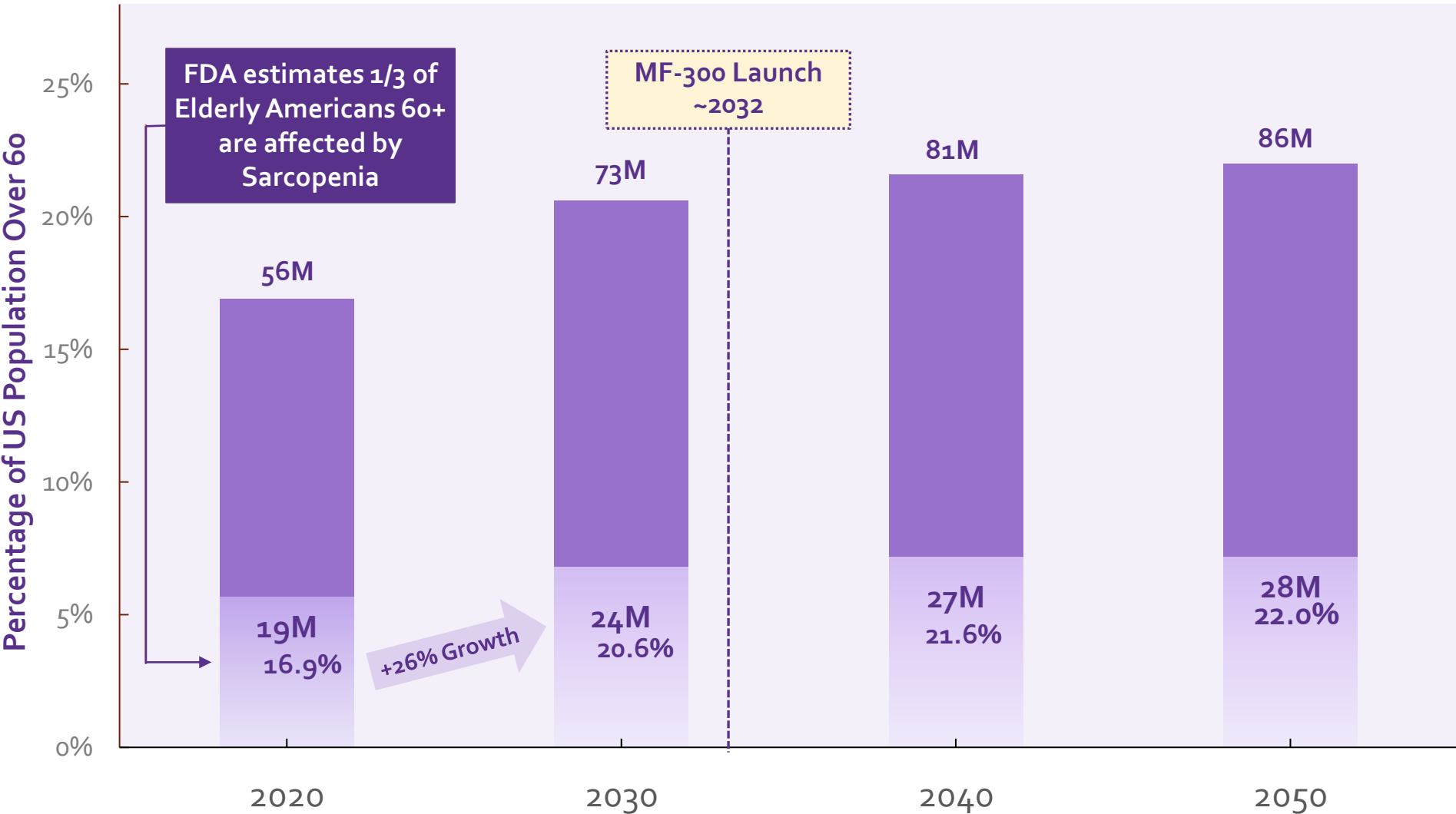
Dependence
~7 million seniors
“at-risk” of losing
independence



Falls
Increased
Morbidity &
Mortality



Mortality
Increased risk
of death



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

Sarcopenia:

- Severe loss of muscle strength and mass with aging
- Strength declines faster than muscle mass¹ 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 aging¹

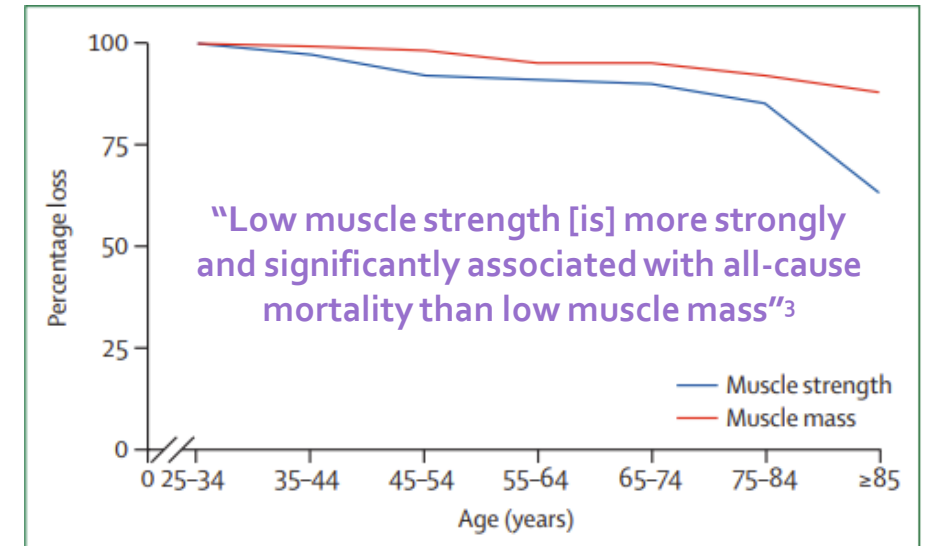


Figure 1: Percentage loss of muscle mass and muscle strength with age in men

“Maintaining or gaining muscle mass does not prevent aging-associated declines in muscle strength”⁵

¹ Cruz-Jentoft and Sayer, *Lancet*, 2019

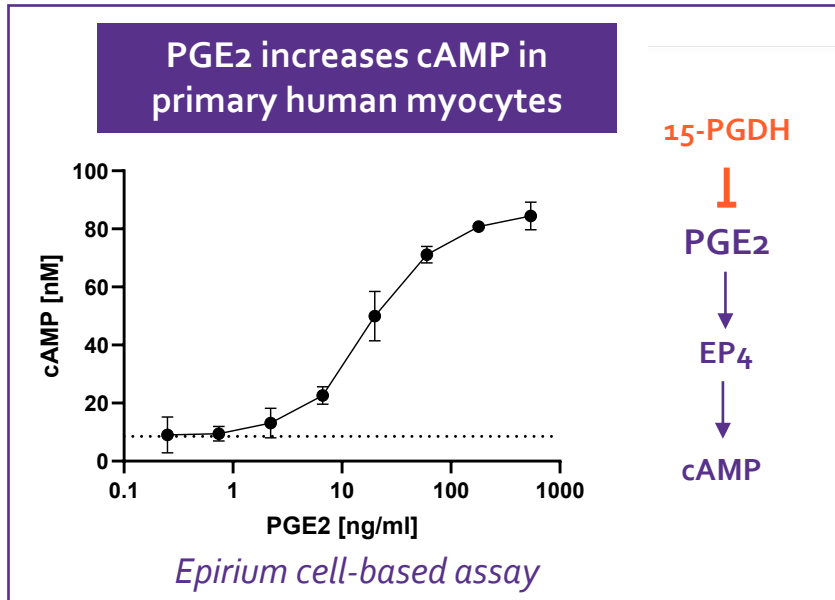
² Jubrias and Conley, *Fun. Neurobio. of Aging*, 2001

³ Li et al., *Med Sci Sports & Exercise*, 2017

⁴ Mohien et al., *eLife*, 2019

⁵ Goodpaster et al., *J Gerontology*, 2006

PGE2 Increases cAMP in Human Muscle Cells & Improves Muscle Function in Aged Mice



Muscle Intrinsic Effects

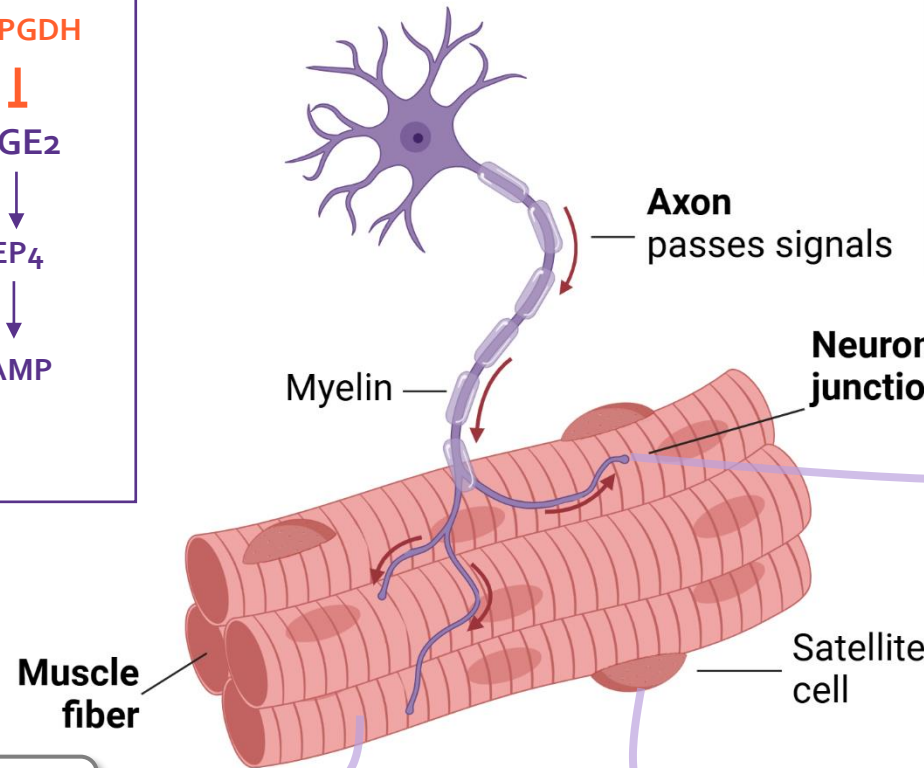
RESEARCH ARTICLE

AGING

Inhibition of prostaglandin-degrading enzyme 15-PGDH rejuvenates aged muscle mass and strength

A. R. Palla^{1,2}, M. Ravichandran^{1,2}, Y. X. Wang^{1,2}, L. Alexandrova⁴, A. V. Yang^{1,2}, P. Kraft^{1,2}, C. A. Holbrook^{1,2}, C. M. Schürch^{2,3}, A. T. V. Ho^{1,2*}, H. M. Blau^{1,2†}

Science



NMJ Integrity

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

MUSCLE PHYSIOLOGY

Regeneration of neuromuscular synapses after acute and chronic denervation by inhibiting the gerozyme 15-prostaglandin dehydrogenase

Mohsen A. Bakooshli^{1†}, Yu Xin Wang^{1,2+*}, Elena Monti¹, Shiqi Su¹, Peggy Kraft¹, Minas Nalbandian¹, Ludmila Alexandrova³, Joshua R. Wheeler^{4,5}, Hannes Vogel^{4,5}, Helen M. Blau^{1*}

Stem-Cell Proliferation

Prostaglandin E2 is essential for efficacious skeletal muscle stem-cell function, augmenting regeneration and strength

Andrew T. V. Ho^{a,1}, Adelaida R. Palla^{a,1}, Matthew R. Blake^a, Nora D. Yucel^a, Yu Xin Wang^a, Klas E. G. Magnusson^{a,b}, Colin A. Holbrook^a, Peggy E. Kraft^a, Scott L. Delp^c, and Helen M. Blau^{a,2}

^aBaxter Lab, Stanford Sci Systems, Univ Stanford

Cell Stem Cell

CellPress

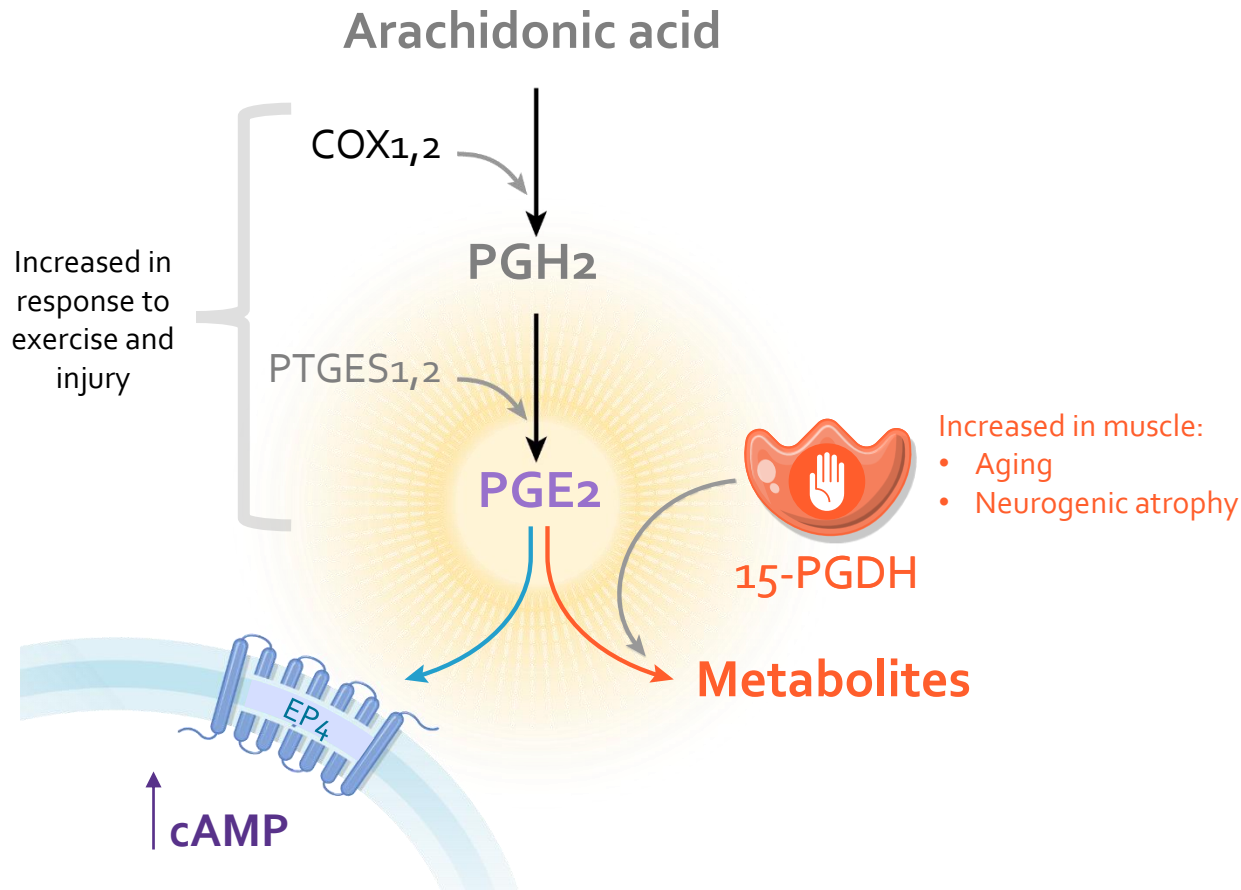
Article

Multimic profiling reveals that prostaglandin E2 reverses aged muscle stem cell dysfunction, leading to increased regeneration and strength

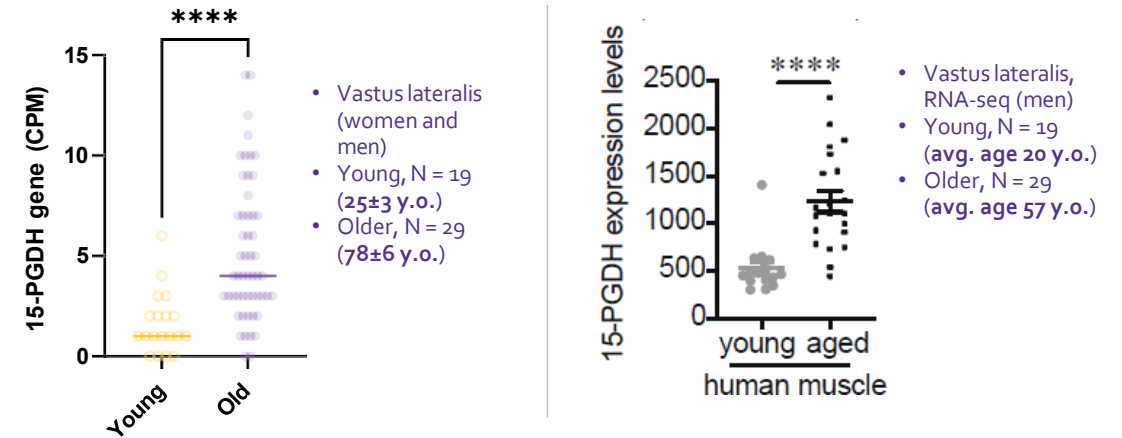
Yu Xin Wang^{1,2,12}, Adelaida R. Palla^{1,12}, Andrew T.V. Ho^{1,12}, Daniel C.L. Robinson¹, Meenakshi Ravichandran¹, Glenn J. Markov¹, Thach Mai¹, Chris Still II^{1,12}, Akshay Balasubramani^{1,12}, Surag Nair¹, Colin A. Holbrook¹, Ann V. Yang¹, Peggy E. Kraft¹, Shiqi Su^{1,12}, David M. Burns^{1,11}, Nora D. Yucel¹, Lei S. Qi^{1,12}, Anshul Kundaje^{1,12} and Helen M. Blau^{1,12,*}

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

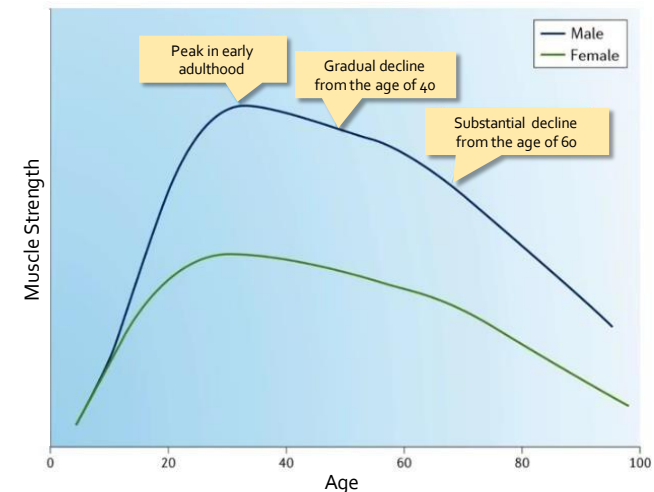
15-HydroxyProstaglandin Dehydrogenase
Metabolically degrades PGE₂



15-PGDH gene expression
Elevated in aged human muscle^{3,4}



Grip strength, a predictor of sarcopenia risk, declines with ages

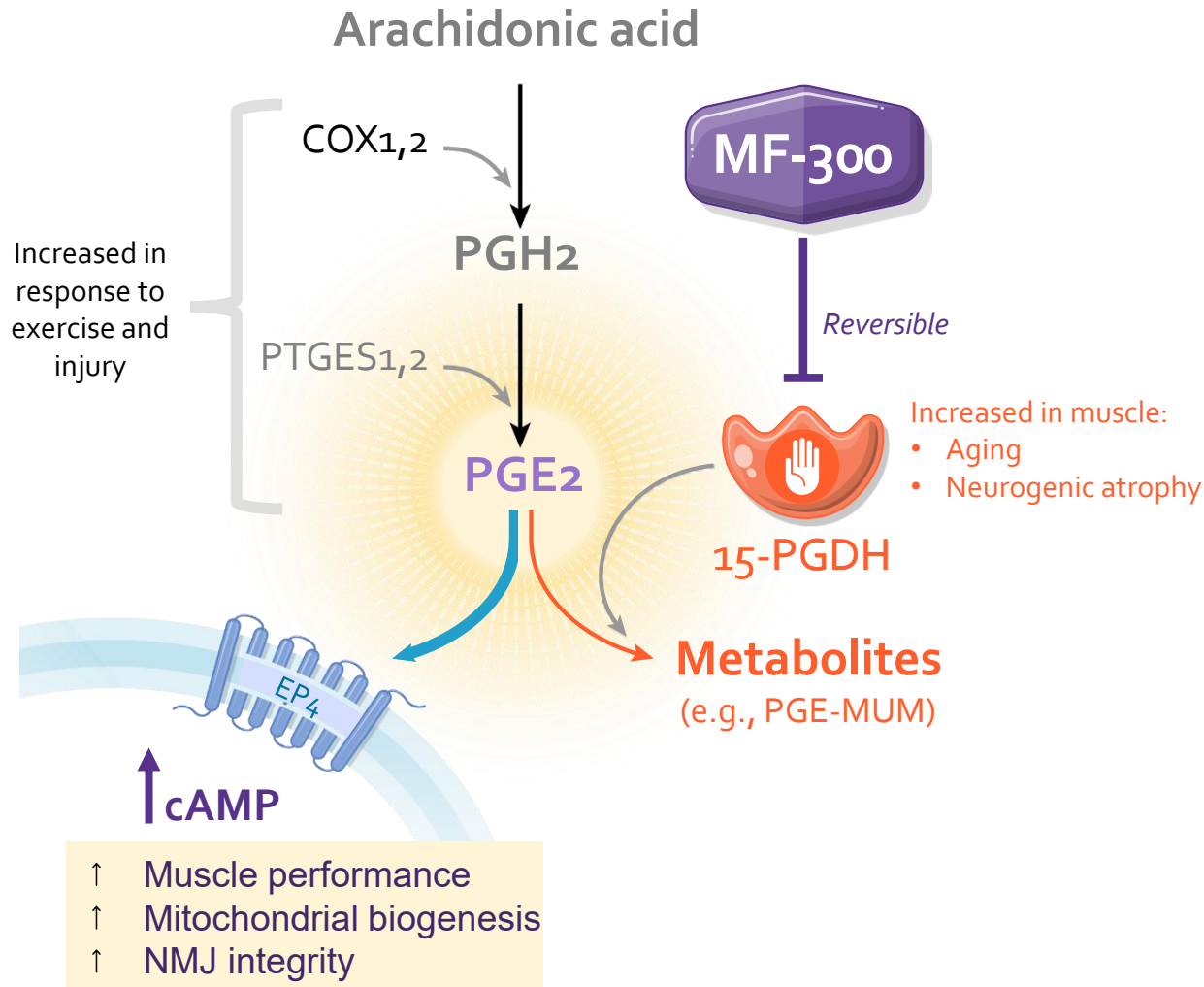


³ GEO167186, ⁴ Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), ⁵ Dennison et al., *Nat Rev Rheum* 2017

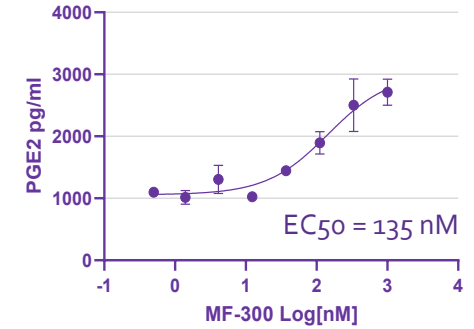
MF-300: Epirium's Therapeutic Strategy to Increase PGE₂ Levels in Aged Muscle

MF-300

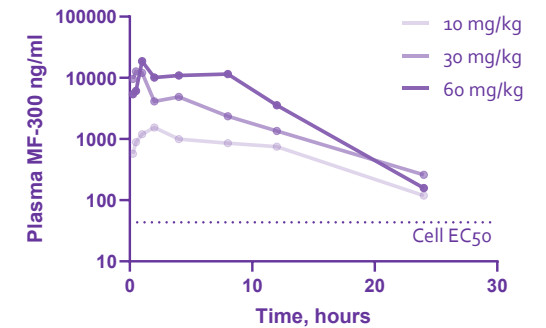
Inhibits 15-PGDH to increase levels of PGE₂



MF-300 increases PGE₂ in cell-based assay



MF-300 is bioavailable and stable in vivo (oral administration)



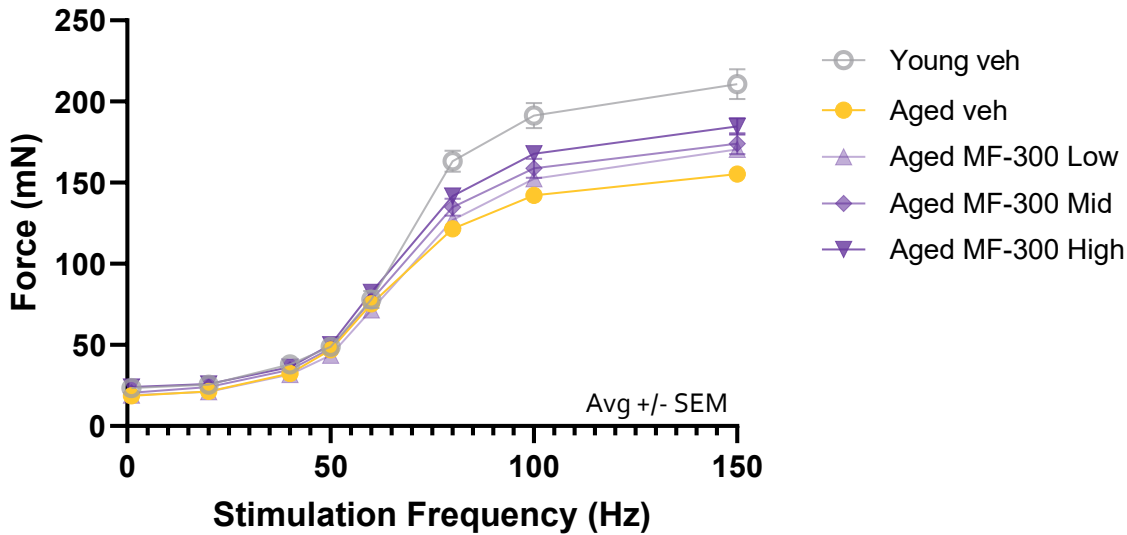
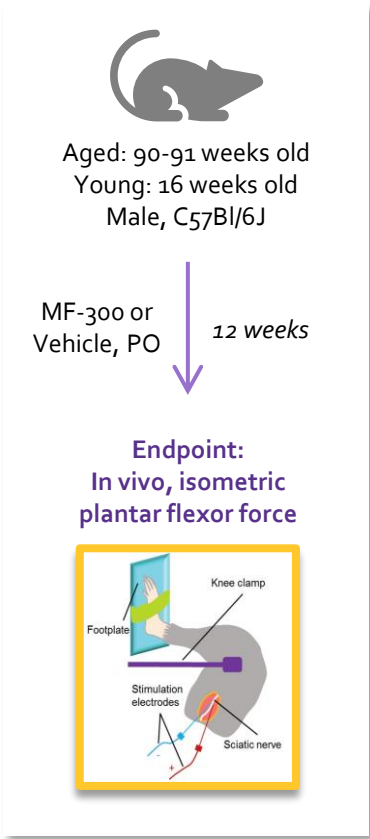
MF-300 Muscle Force Efficacy in Aged Mice with 12-Weeks Oral Administration



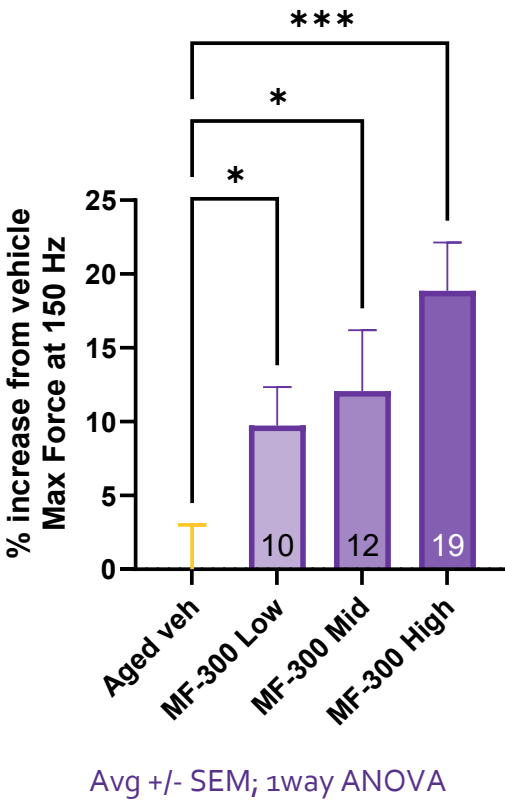
Exposure response observed (based on cumulative 12-week exposure across groups)

Max force of isometric plantar flexion at 12 weeks

% increase over veh at 150 Hz



Aged veh vs:	2way ANOVA w/ Dunnett's multiple comparisons test
MF-300 Low	ns
MF-300 Mid	p < .0001
MF-300 High	p < .0001

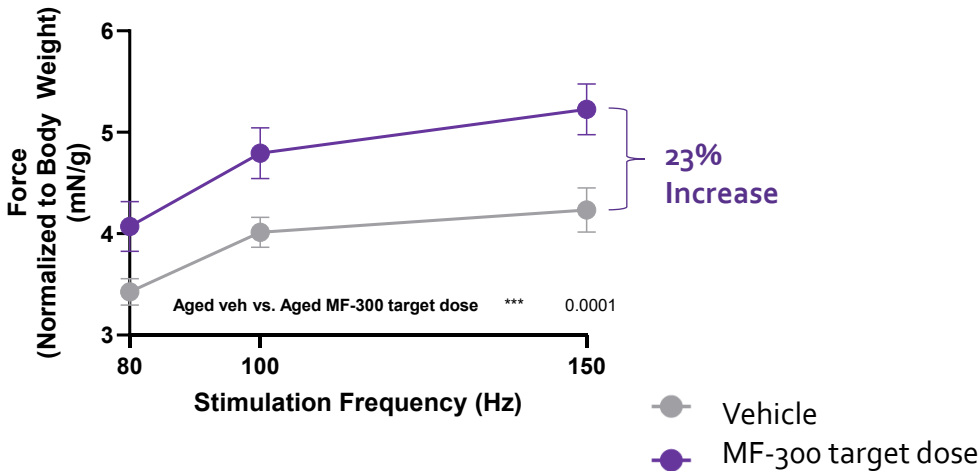


MF-300 Increases Muscle Force with Correlated Reduction in PD Biomarker

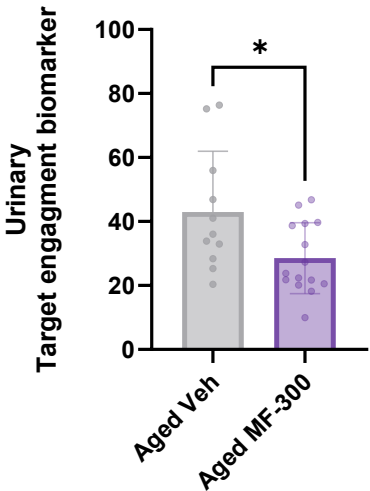


MF-300 Increased muscle force in aged mice

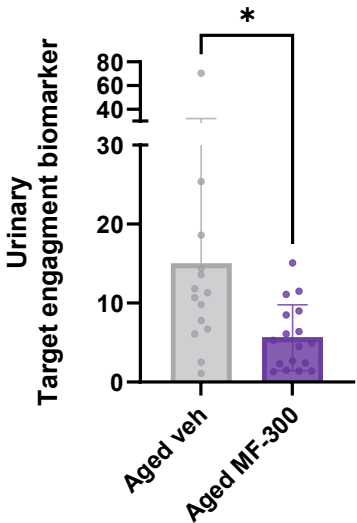
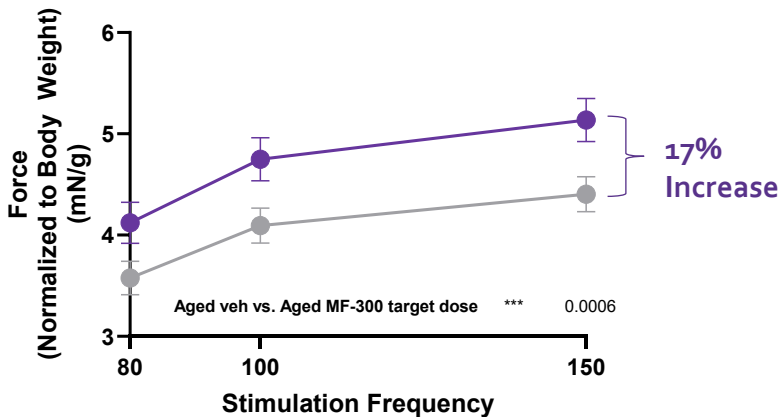
Study 1



MF-300 Reduced urinary metabolite of PGE₂



Study 2



Monotherapy preclinical efficacy

- **Sarcopenia: age-related muscle weakness - MF-300 Lead Indication**
- Nerve Injury

Combination Therapy preclinical efficacy

- **Rare Neuromuscular Disease with Standard of Care (SOC) i.e., disease modifying**
 - Well established proof-of-concept in disease models of Spinal Muscular Atrophy (SMA)
 - Rationale for indication expansion: DMD, FSHD, Myasthenia Gravis

“Next Generation” muscle enhancement

- **Proof-of-principle combination with myostatin inhibitor**
 - Additive/synergistic effect increasing functional muscle mass in SMA model
- **High-value areas of opportunity to explore**
 - Sarcopenic Obesity (i.e., with GLP weight loss)
 - Rare disease + SOC with severe residual unmet need

Clinical Update

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

Financials & Wrap-up

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

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

Overview

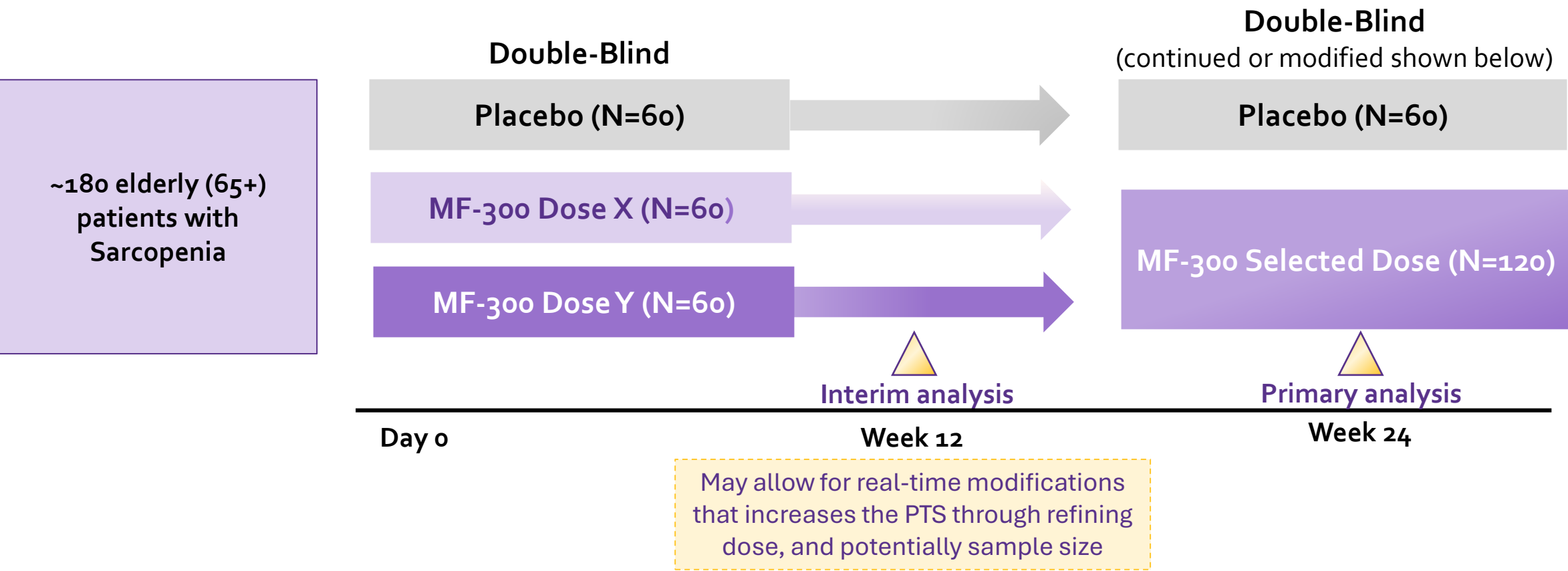
24 week randomized, double-blind, placebo-controlled, adaptive design

Interim Analysis

Analysis 20/arm at Week-12

Primary Analysis

Potential PE: Timed 5xs Chair Stand; Secondary Endpoints: e.g., Muscle Strength, SPPB, PROs



Entry Criteria

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

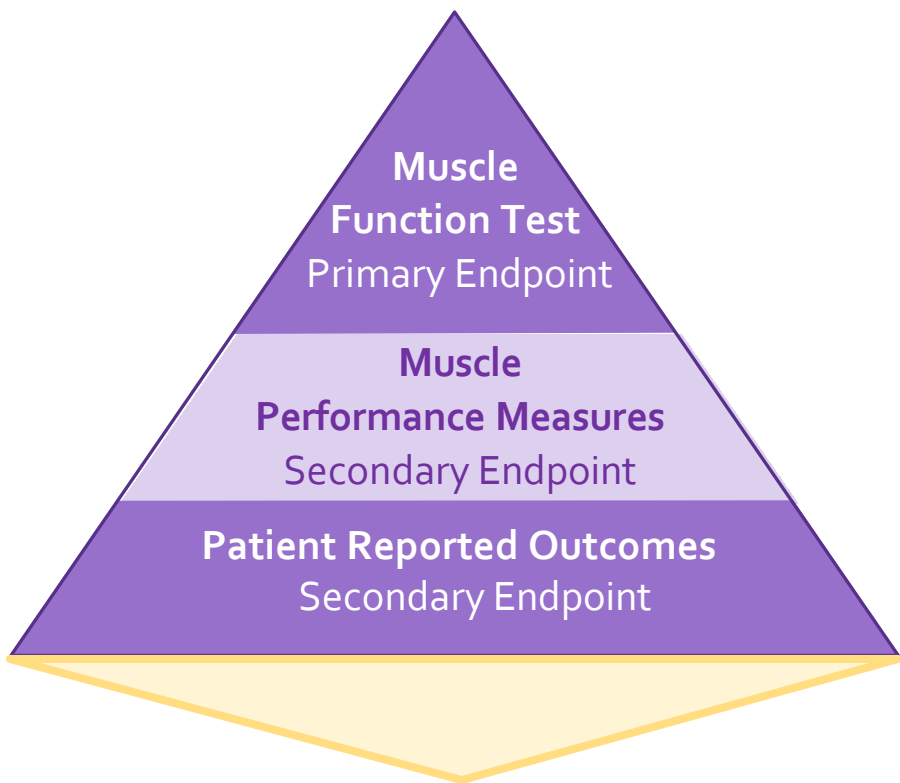
- Low grip strength (< 35.5 kg for men, < 20 kg for women) &
- Slowness (walking speed < 0.8 m/s)
- SPPB* Score 4 – 8
- Poor performance on 5xs chair stand test

***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.

Totality of Evidence to Support Sarcopenia Indication



Meaningful Patient Benefit

Endpoints

Primary Endpoint:

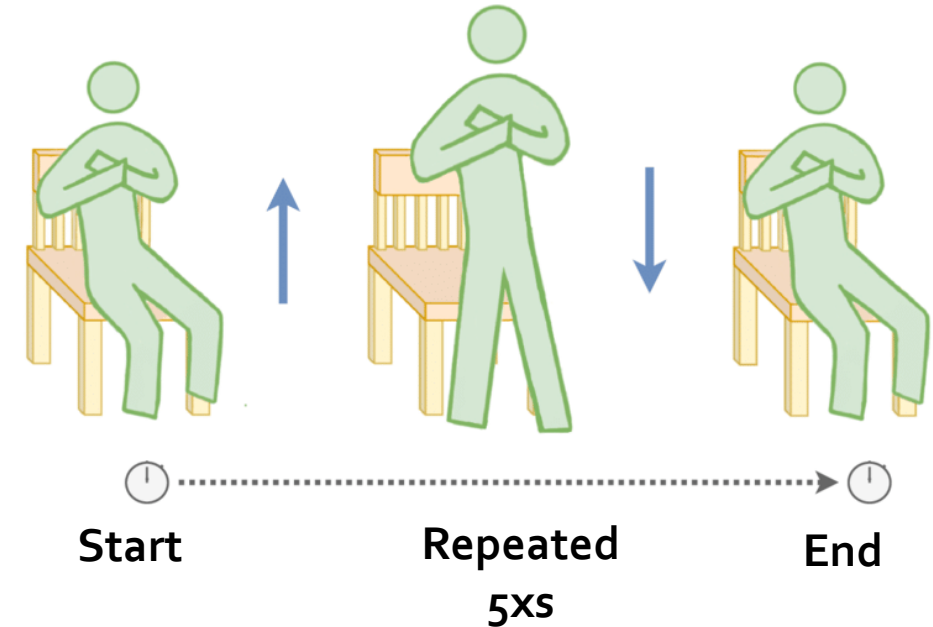
CFB vs. PBO
5xs Chair Stand Test (sec)

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

- **Accepted proxy measure of lower limb power and strength**
 - Endorsed by World Health Organization (WHO) ICOPE¹ & EWGSOP²
 - Core component of SPPB³
- **Strong predictor of clinical outcomes**
 - Activities of daily living
 - Fall Risk
 - All-Cause Mortality
- **Assesses Locomotor Capacity, a key domain of Intrinsic Capacity (IC)**
- **Loss of 1 second (~10%) per year is considered clinically significant**

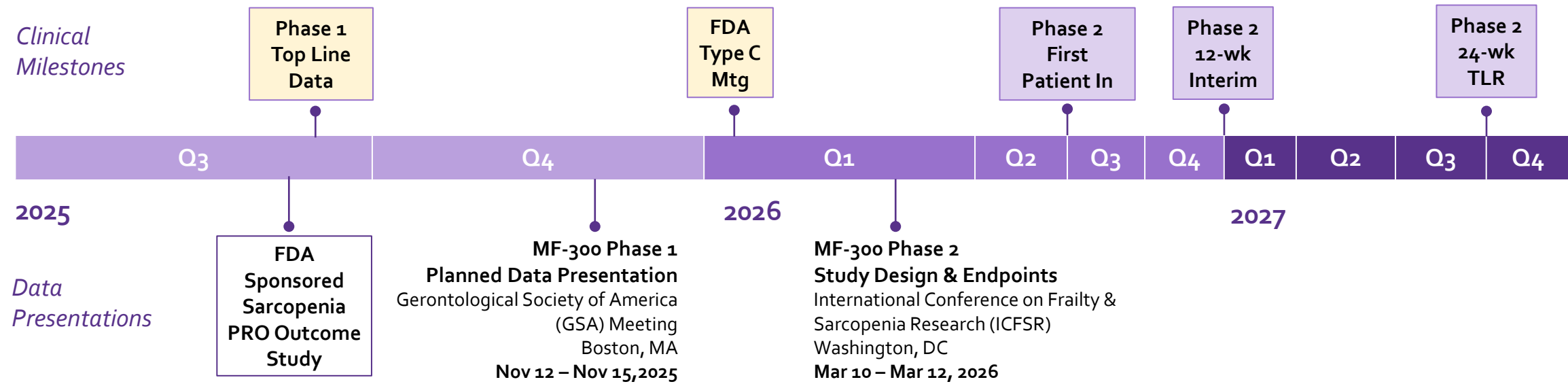


1. ICOPE=Integrated Care for Older People ([9789240103726-eng.pdf](#))

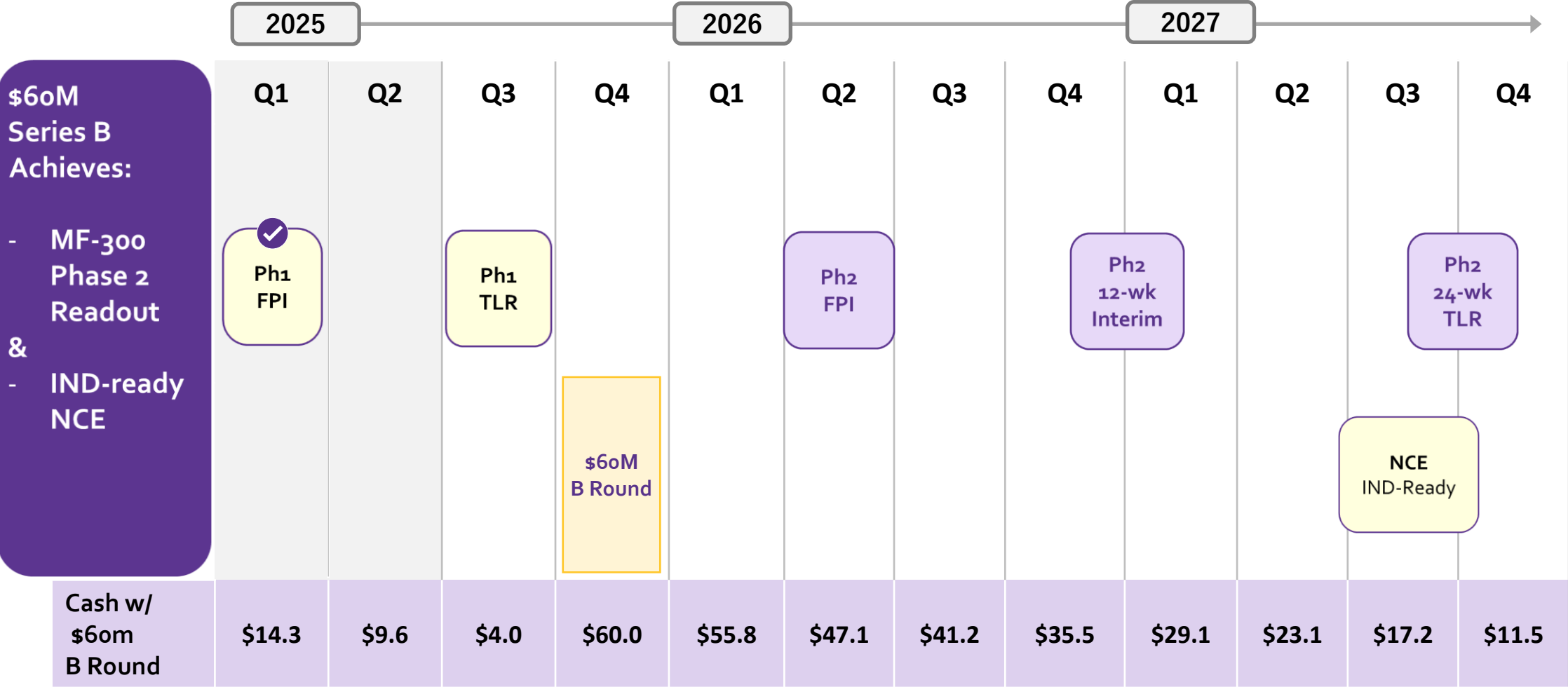
2. EWGSOP2=European Working Group on Sarcopenia in Older People 2 (CRUZ-JENTOFT AJ, et al. Age and Aging. 2019;48:16-31).

3. Short Physical Performance Battery

Key MF-300 Phase 1 & 2 Clinical Milestones & External Activities



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



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
-



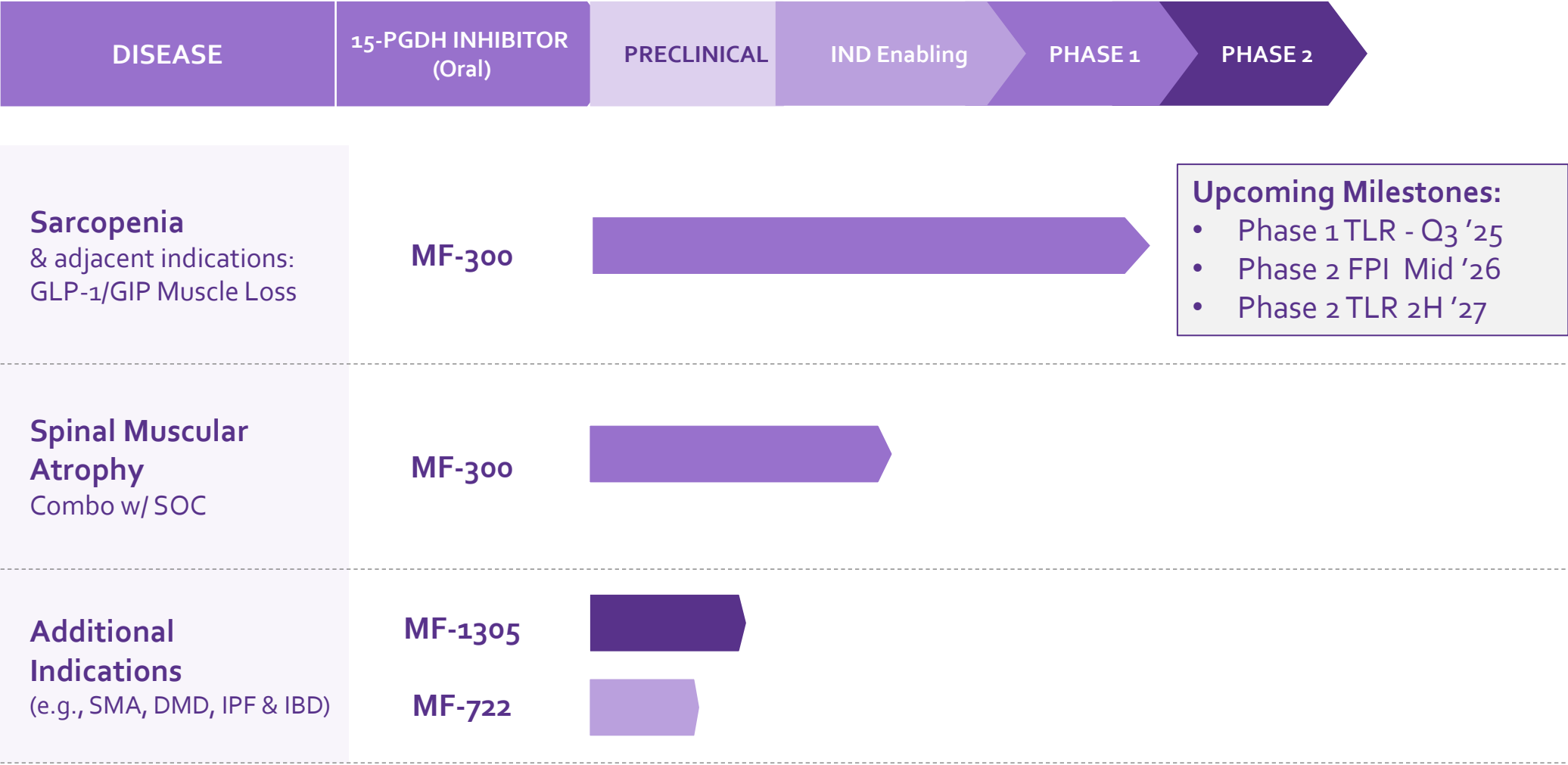
MF-300 + MSTNi Muscle Mass & Force Efficacy in $\Delta 7$ SMA Model

- 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”





Thank you!

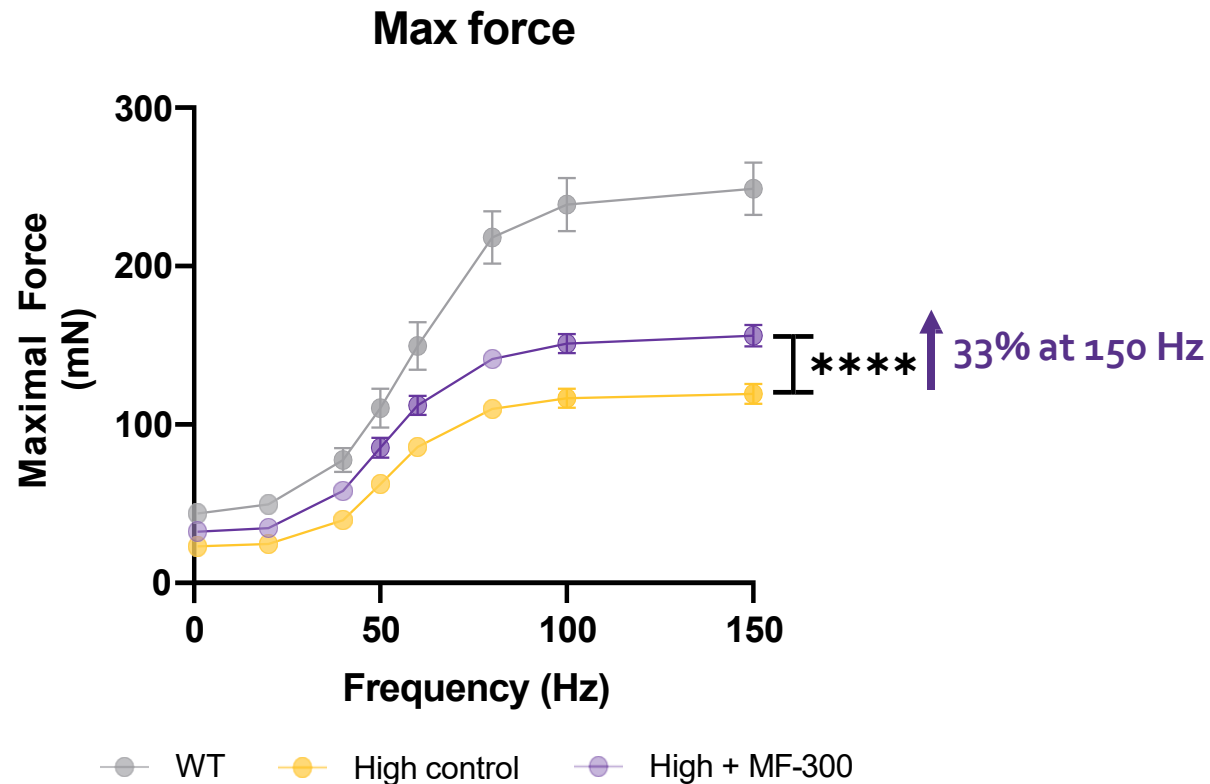
www.epirium.com

info@epirium.com

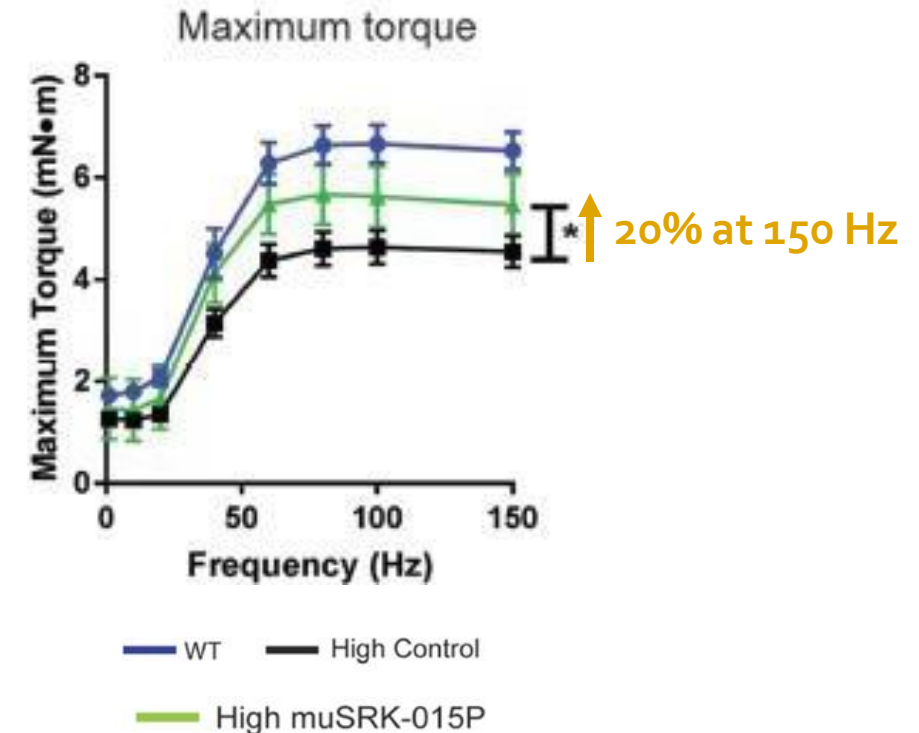
Spinal Muscular Atrophy Recent Data Review:

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

MF-300 in SMN Δ 7 High/High Male mice



mSRK-015P in mouse Δ 7 High/High Male and female mice

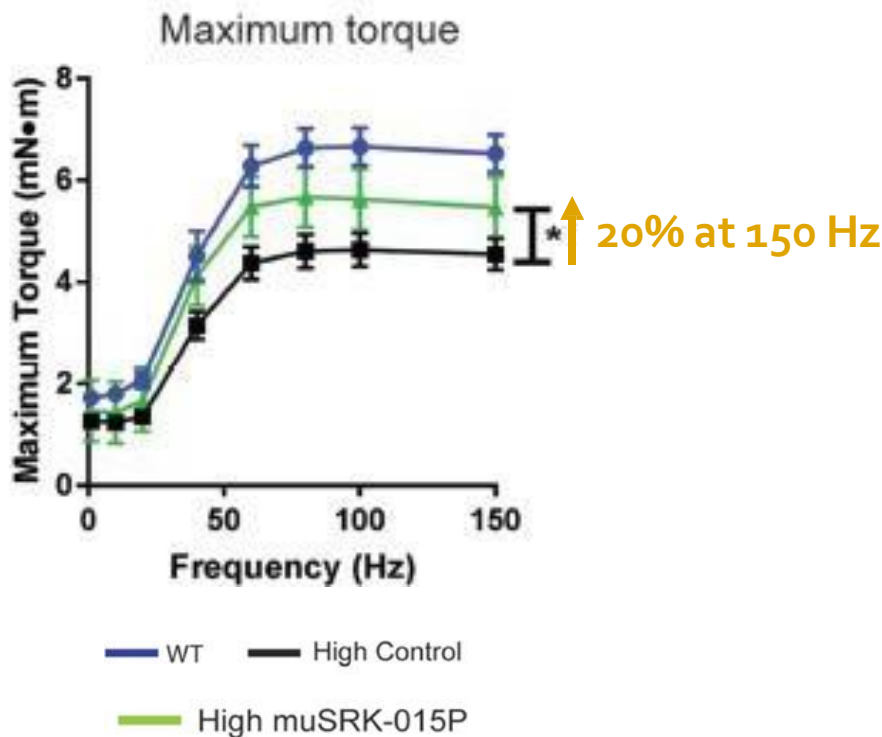


Force = Torque

MYOLOGICA

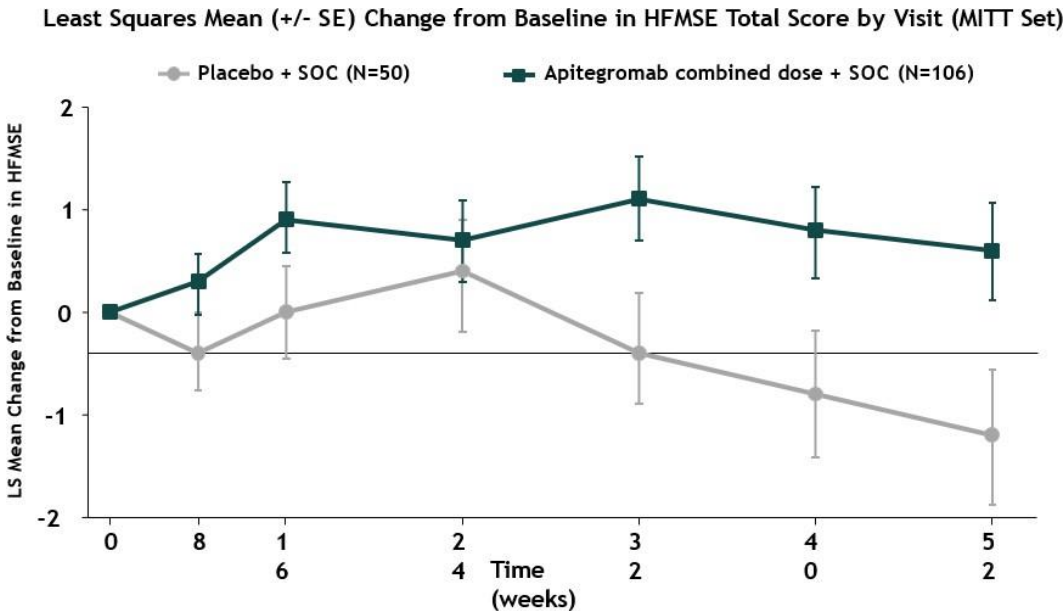
Demonstrates that a 20% increase in isometric plantar flexor force in mice translates to clinical benefit

mSRK-o15P in mouse Δ7 High/High



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

Apitegromab in SMA + SOC (Ph 3 SAPHIRE)



Change from Baseline in HFMSE Total Score

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

Primary Analysis

Achieved Statistical Significance