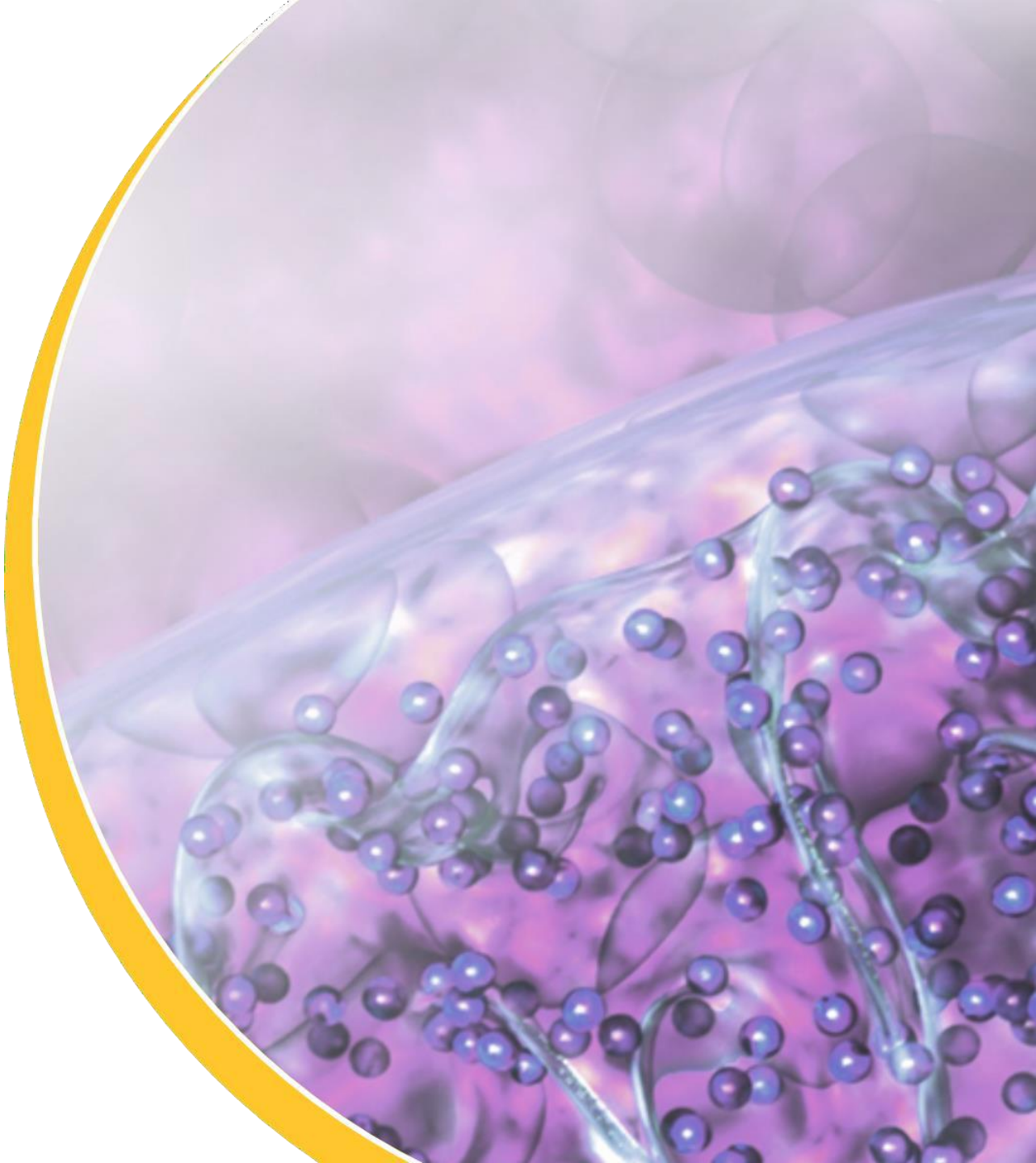
Epirium Bio

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, 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

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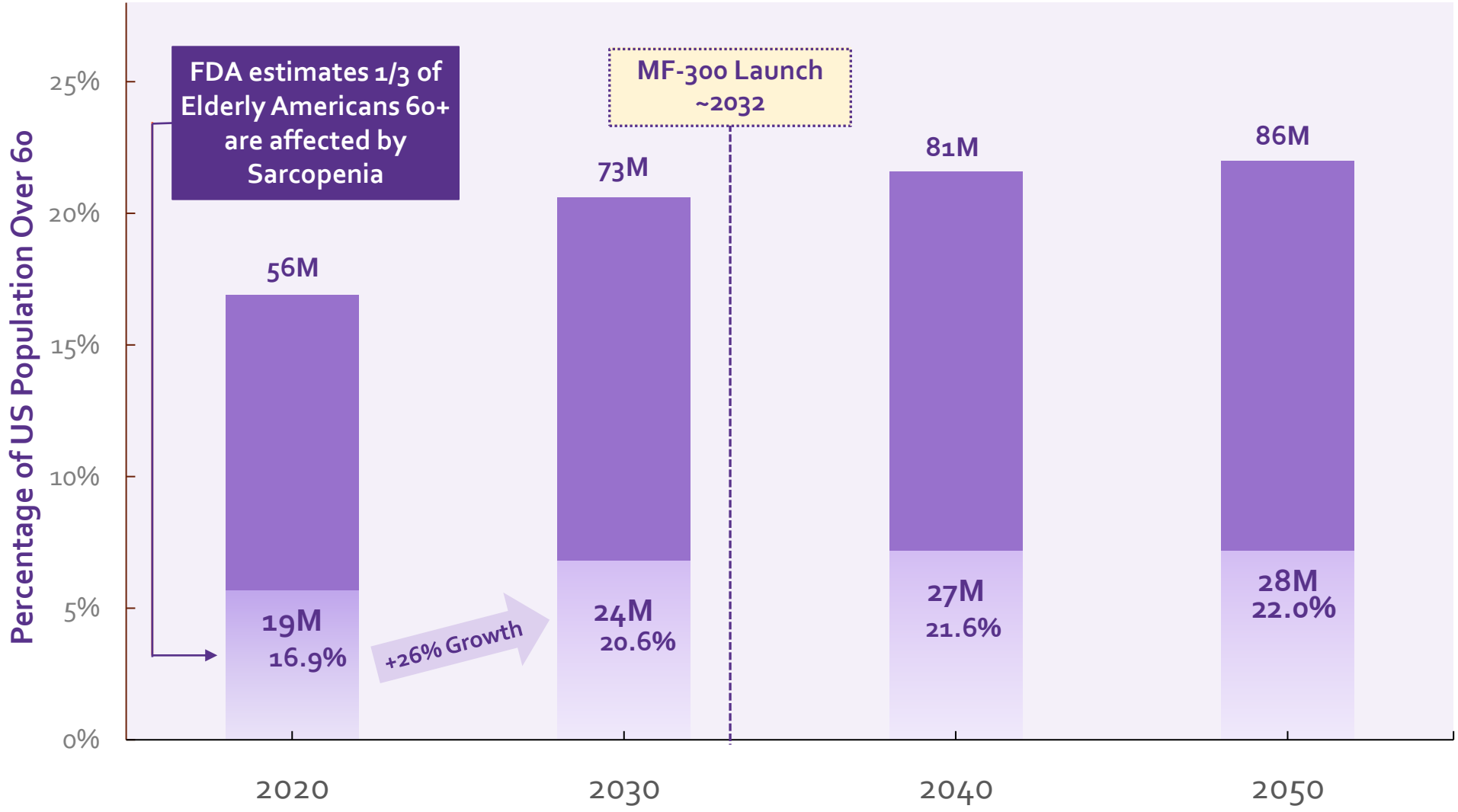
Current U.S. Healthcare Sarcopenia Spending Estimated >$40 Billion Annually

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 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]

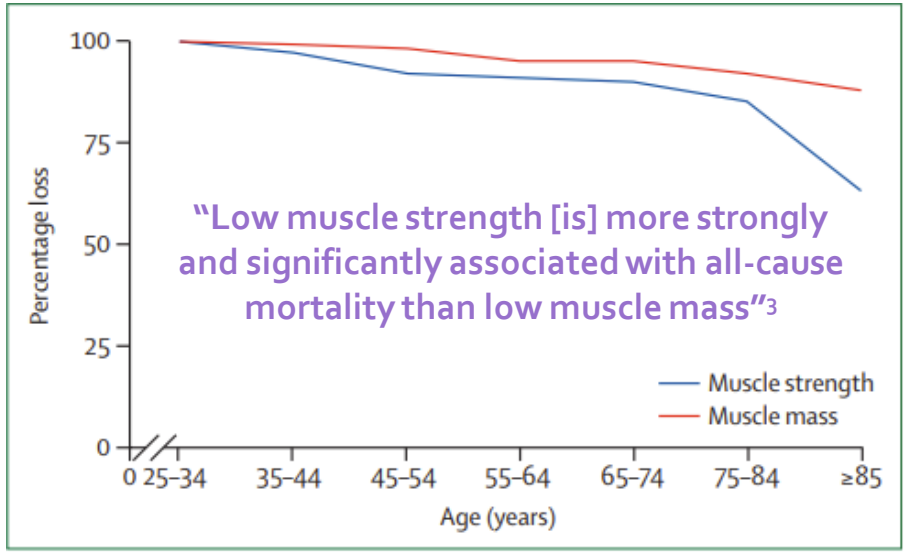

Figure 1: Percentage loss of muscle mass and muscle strength with age in men

"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

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

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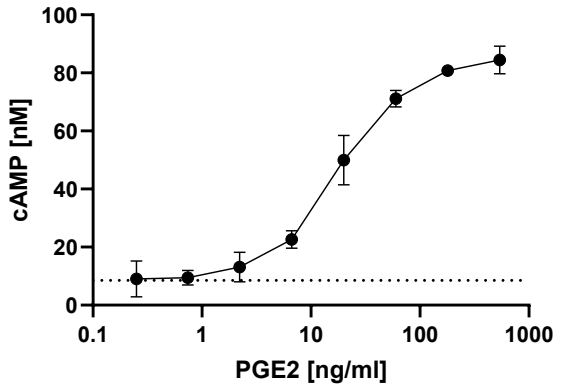
PGE2 increases cAMP in primary human myocytes



Epirium cell-based assay

15-PGDH ⊣ PGE2 → EP4 → cAMP

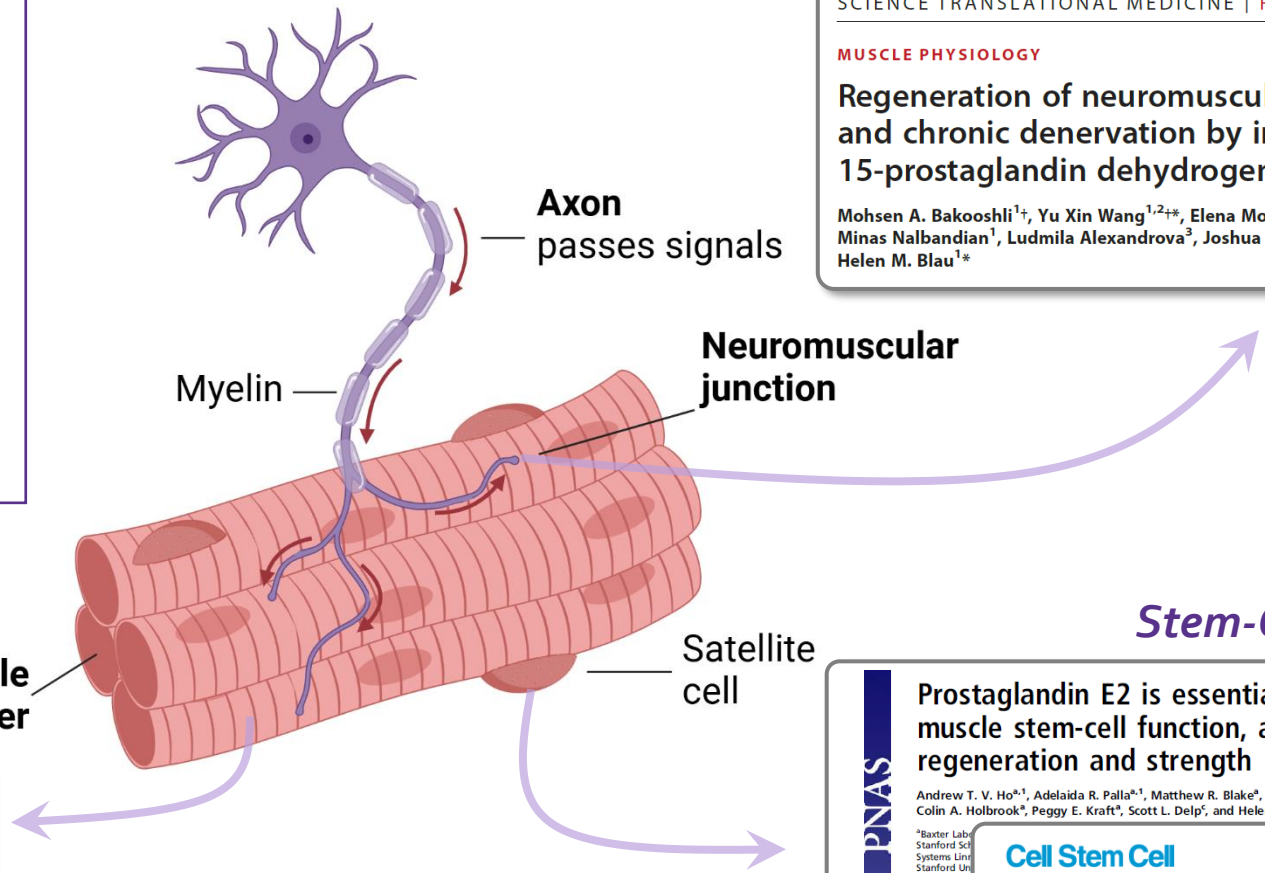
NMJ Integrity

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 Monti[1], Shiqi Su[1], Peggy Kraft[1], Minas Nalbandian[1], Ludmila Alexandrova[3], Joshua R. Wheeler[4,5], Hannes Vogel[4,5], Helen M. Blau[1*]



Muscle Intrinsic Effects

RESEARCH ARTICLE

Science

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. Alexandrova[4], 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]†

Stem-Cell Proliferation

PNAS

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]

Cell Stem Cell

CellPress

Article

Multiomic 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,[1,8,12] Daniel C.L. Robinson,[1] Meenakshi Ravichandran,[1] Glenn J. Markov,[1] Thach Mai,[1] Chris Still II,[3,10] Akshay Balsubramani,[4,5] Surag Nair,[4] Colin A. Holbrook,[1] Ann V. Yang,[1] Peggy E. Kraft,[1] Shiqi Su,[1,2] David M. Burns,[1,11] Nora D. Yucel,[1] Lei S. Qi,[6,7,8] Anshul Kundaje,[4,9] and Helen M. Blau[1,13,*]

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

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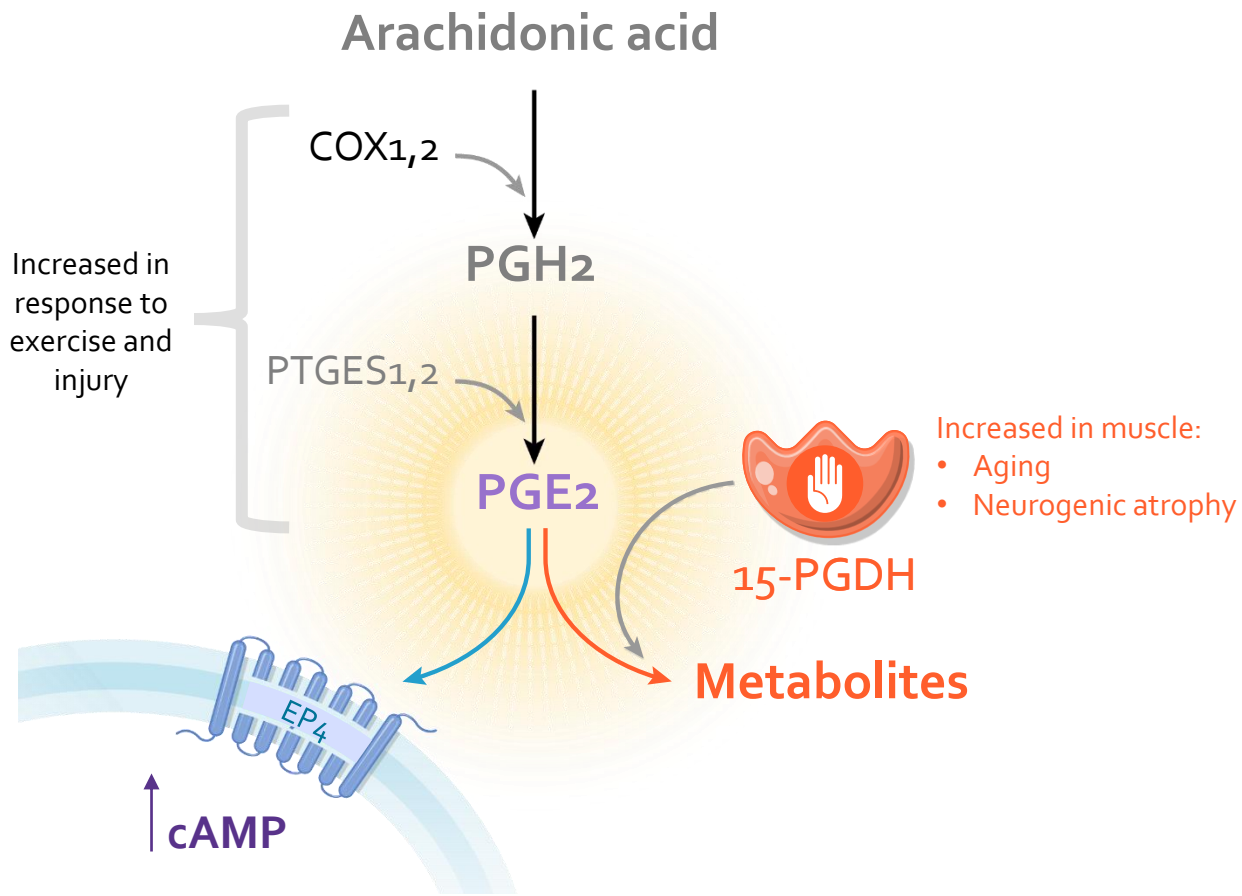
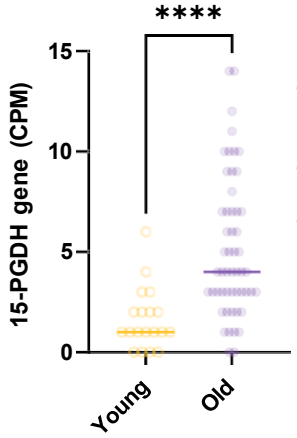
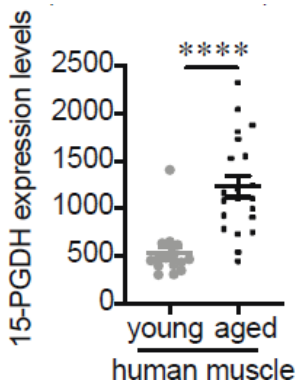
15-HydroxyProstaglandin Dehydrogenase Metabolically degrades PGE2



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

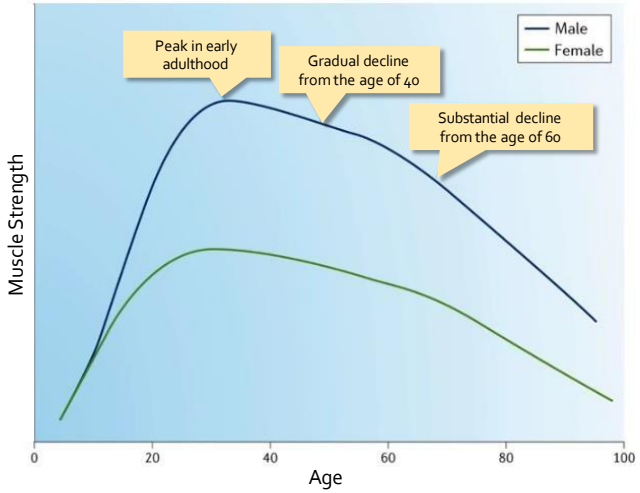


- Vastus lateralis (women and men)
- Young, N = 19 (**25±3 y.o.**)
- Older, N = 29 (**78±6 y.o.**)



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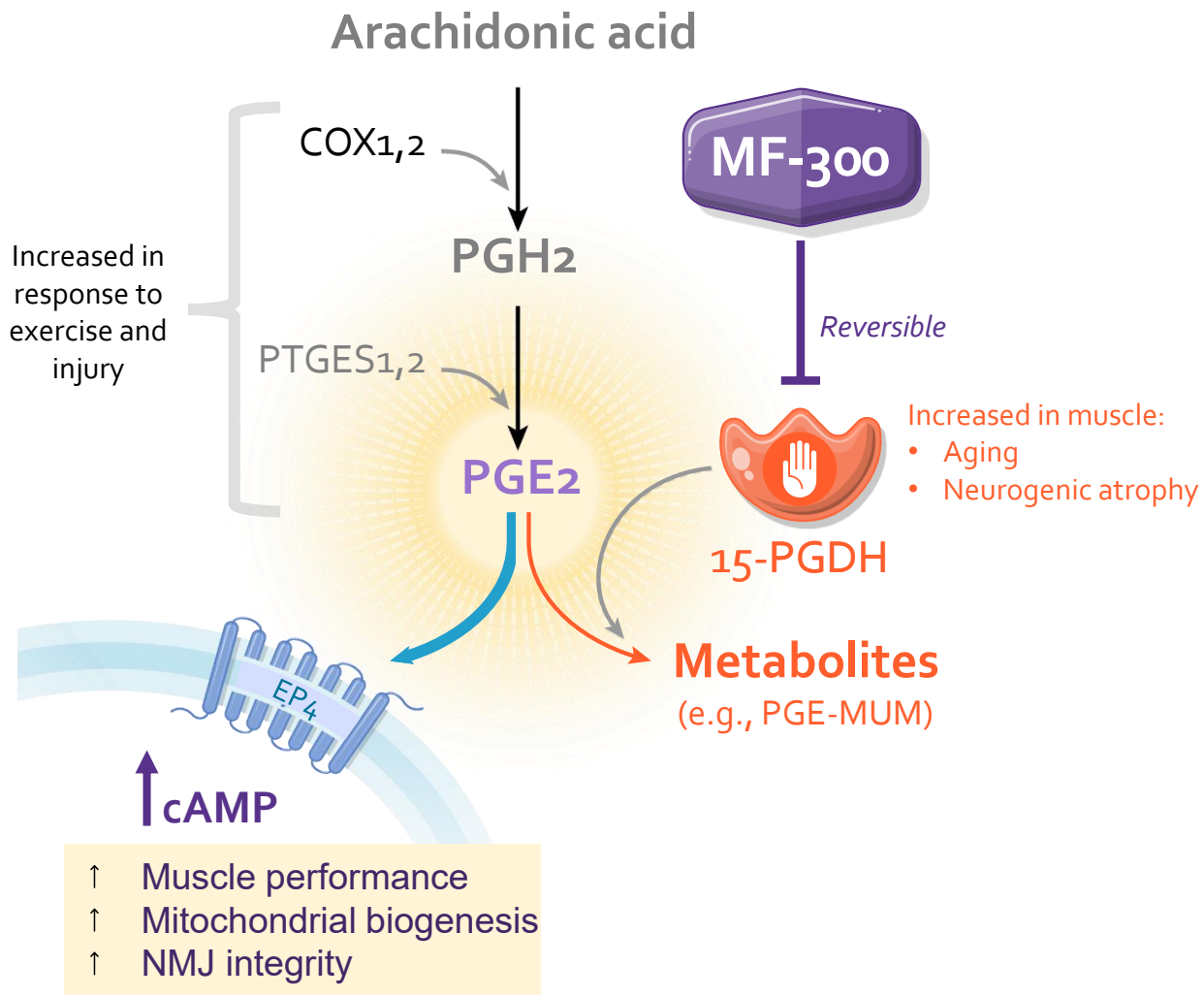
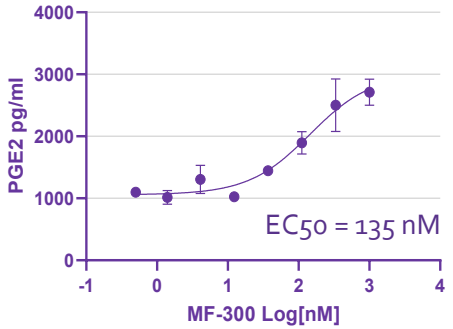
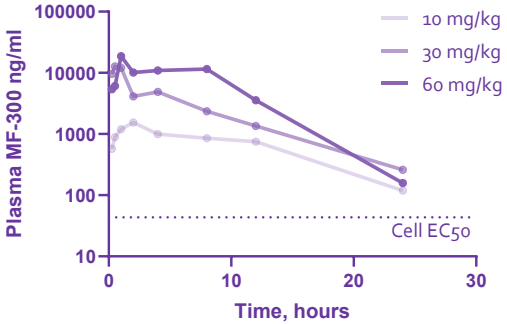
MF-300
Inhibits 15-PGDH to increase levels of PGE2



MF-300 increases PGE2 in cell-based assay



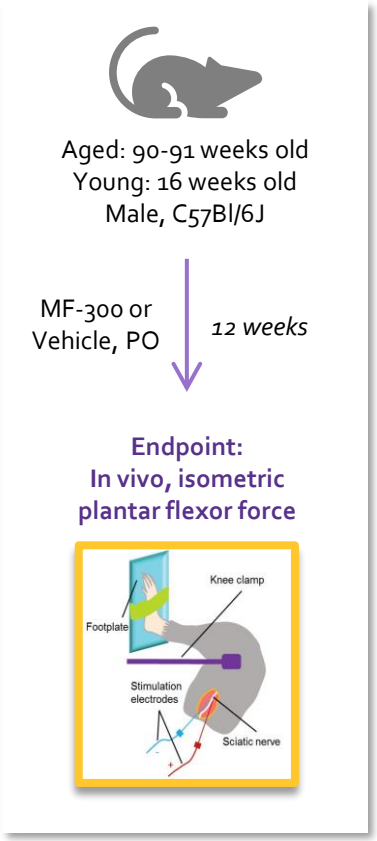
MF-300 is bioavailable and stable in vivo (oral administration)

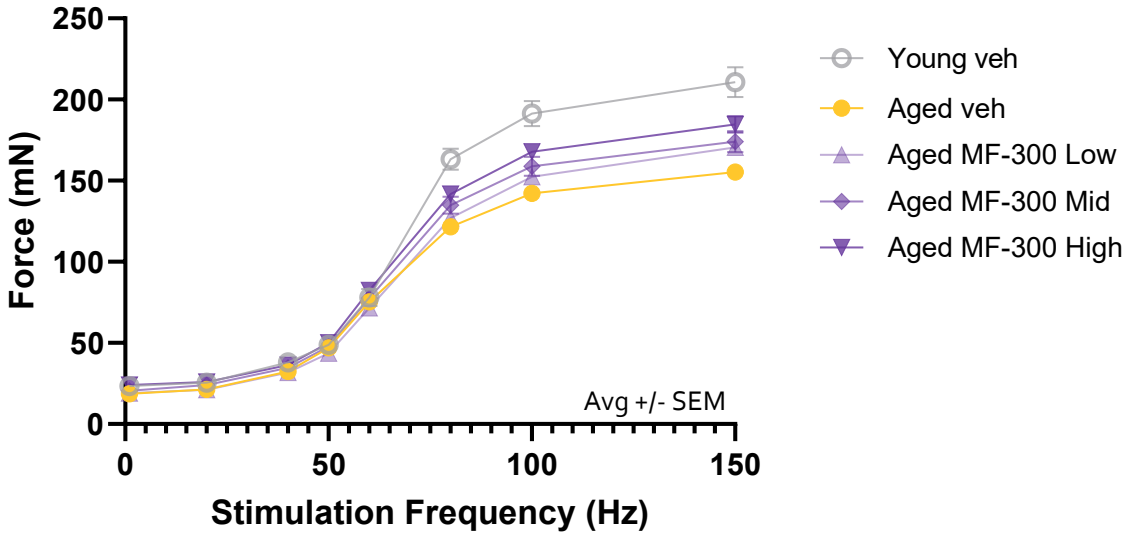


MF-300 Muscle Force Efficacy in Aged Mice with 12-Weeks Oral Administration

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

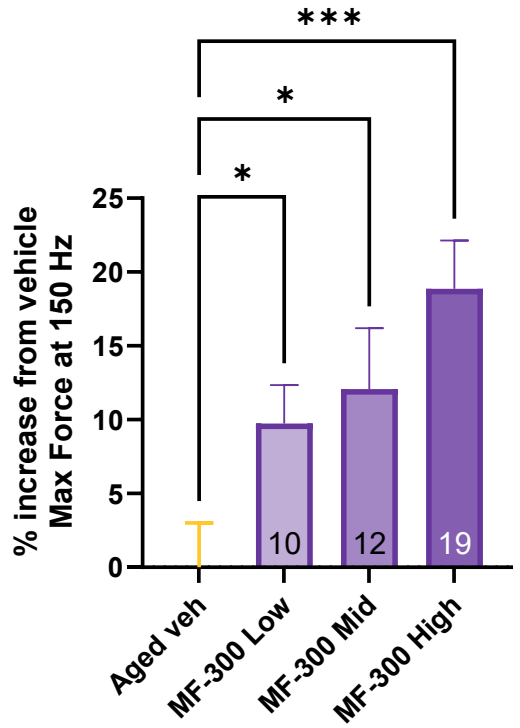
Max force of isometric plantar flexion at 12 weeks





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

% increase over veh at 150 Hz



Avg +/- SEM; 1way ANOVA

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

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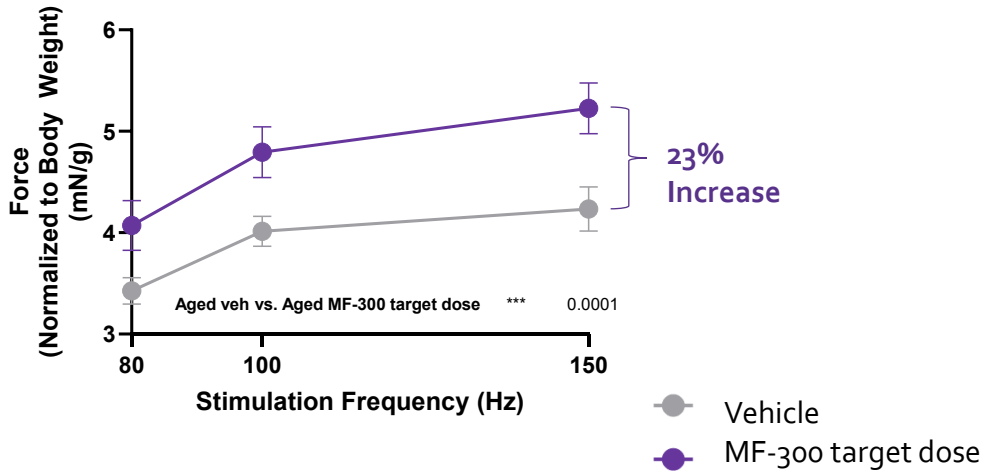
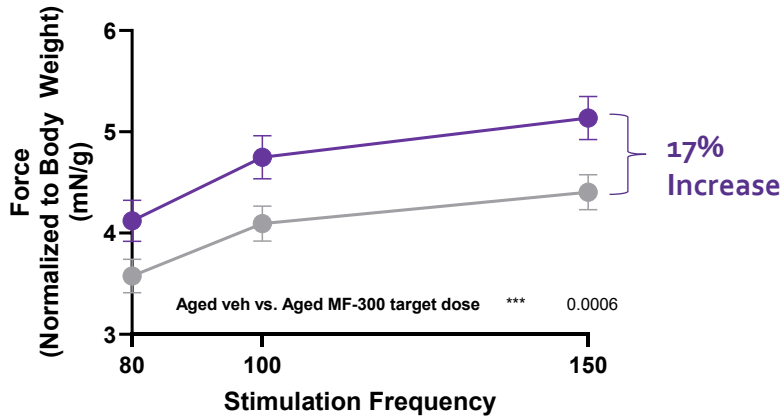
MF-300 Increased muscle force in aged mice

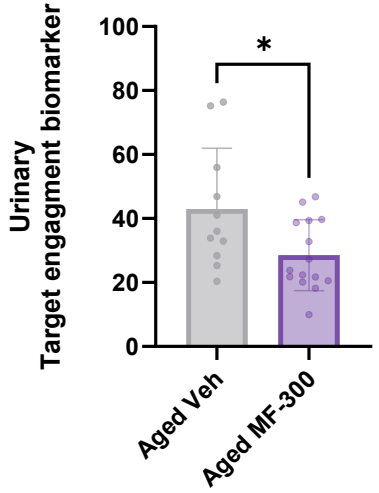
Study 1

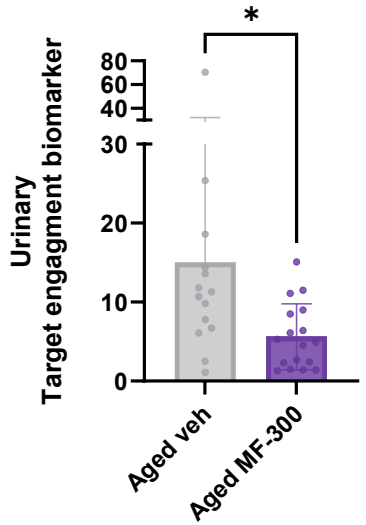


Study 2



MF-300 Reduced urinary metabolite of PGE2





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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

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Overview

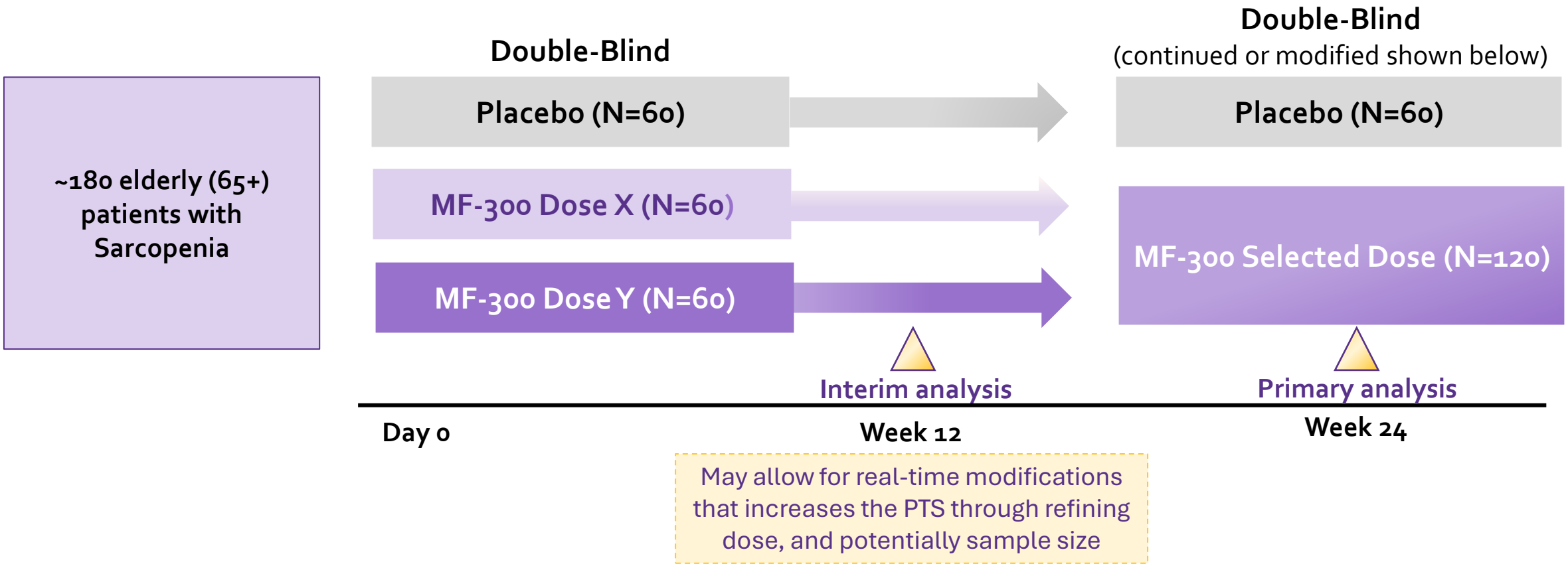
24 week randomized, double-blind, placebo-controlled, adaptive design

Interim Analysis

Analysis 20/arm at Week-12

Primary Analysis

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



May allow for real-time modifications that increases the PTS through refining dose, and potentially sample size

Phase 2 Planning: Entry Criteria & Indication Relevant Endpoints

Entry Criteria

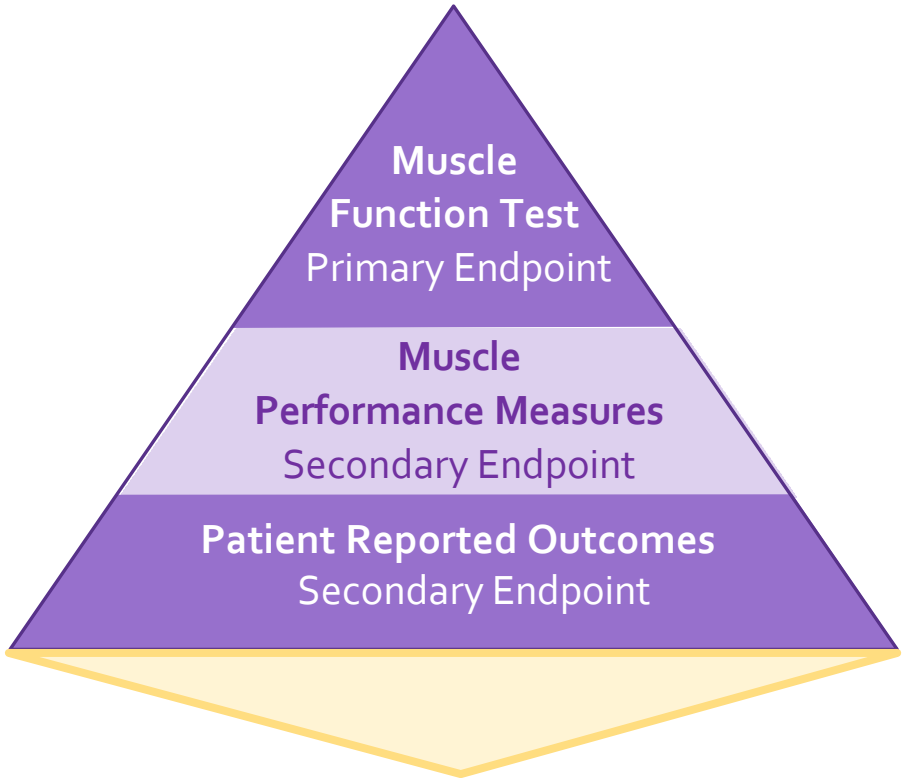
Elderly (≥65 yo)[1] men and women with sarcopenia according to SDOC definition:[2]

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

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

Clinical Milestones

Phase 1 Top Line Data

FDA Type C Mtg

Phase 2 First Patient In

Phase 2 12-wk Interim

Phase 2 24-wk TLR

2025 **2026** **2027**

Data Presentations

FDA Sponsored Sarcopenia PRO Outcome Study

MF-300 Phase 1 Planned Data Presentation
Gerontological Society of America (GSA) Meeting
Boston, MA
Nov 12 – Nov 15,2025

MF-300 Phase 2 Study Design & Endpoints
International Conference on Frailty & Sarcopenia Research (ICFSR)
Washington, DC
Mar 10 – Mar 12, 2026

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

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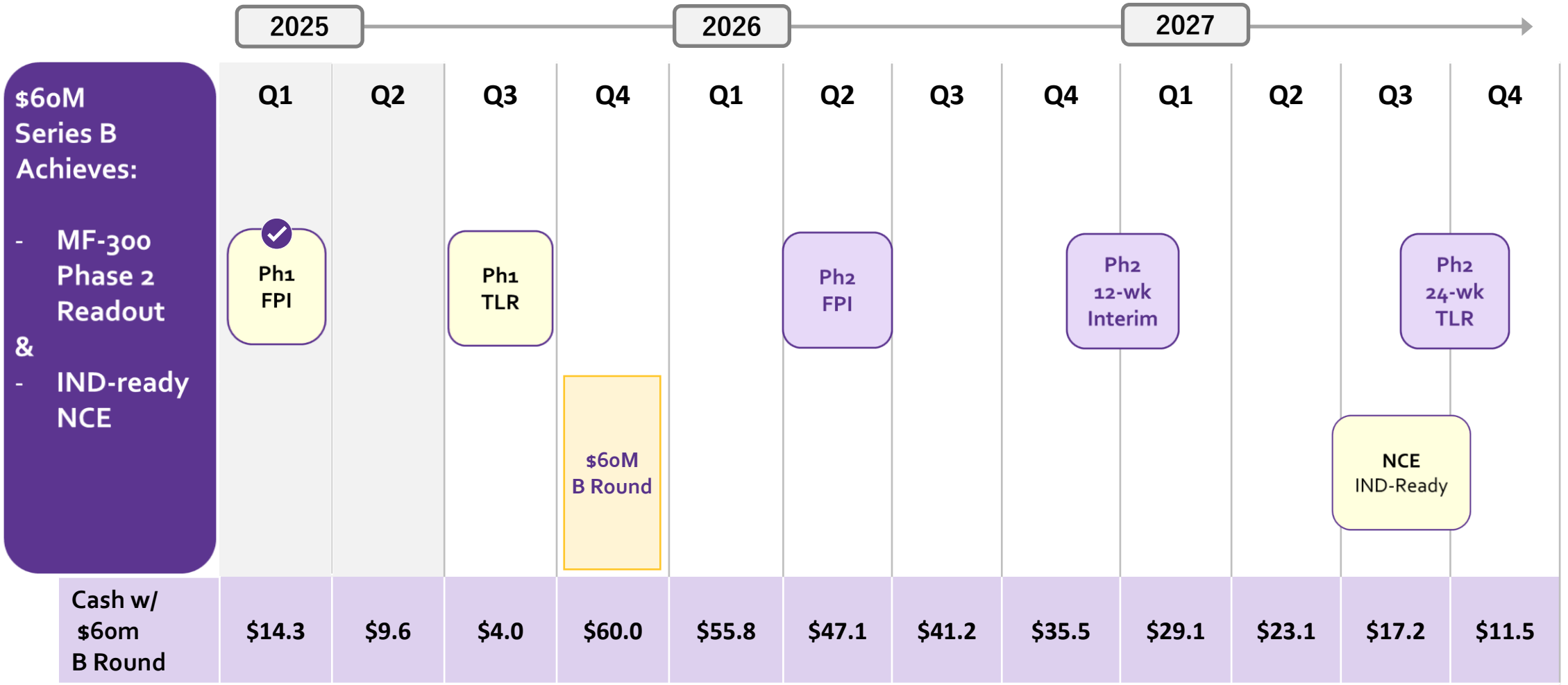

MF-300 Value Creating Milestones over next 6 months

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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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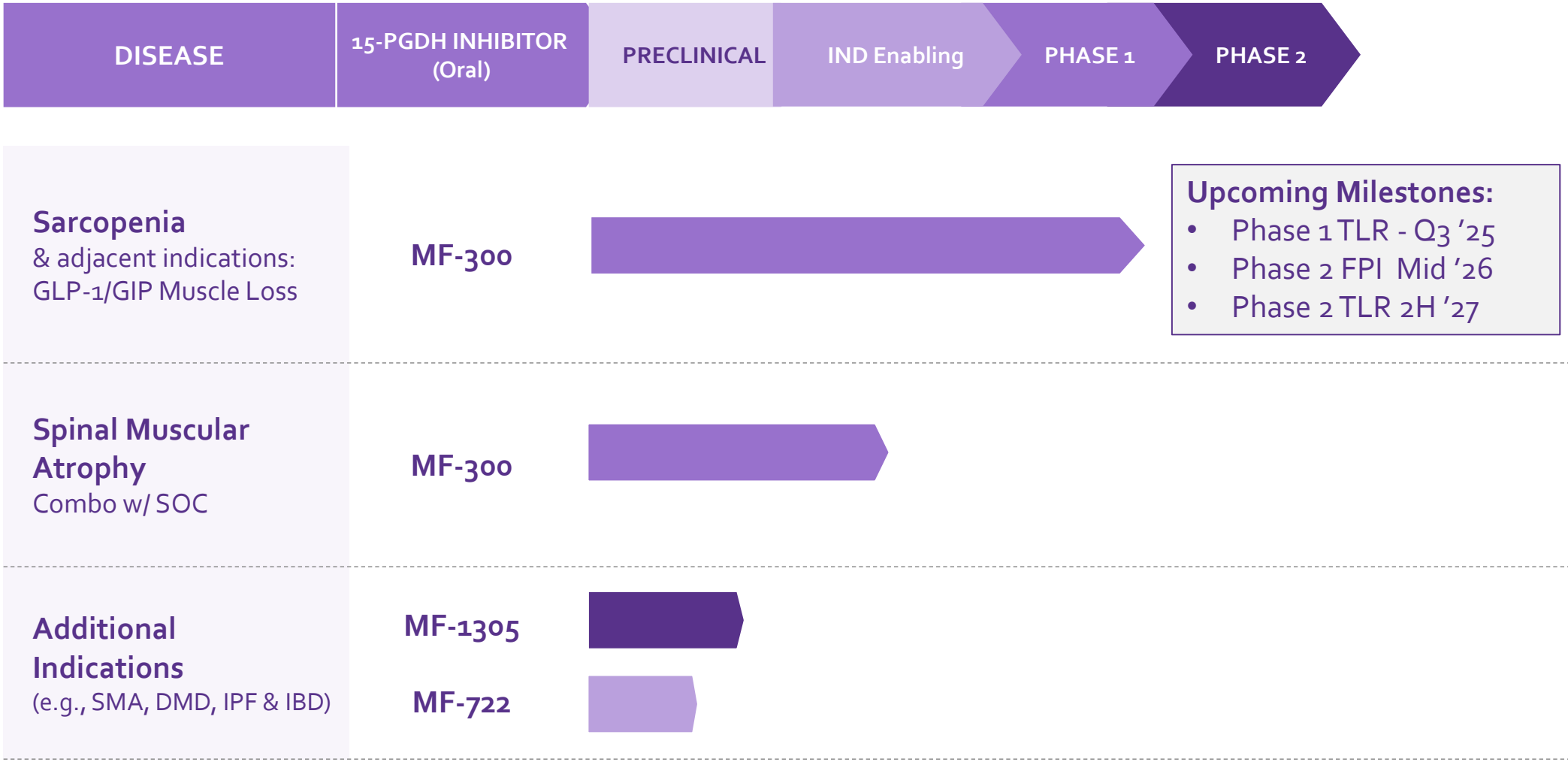

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Thank you!

www.epirium.com

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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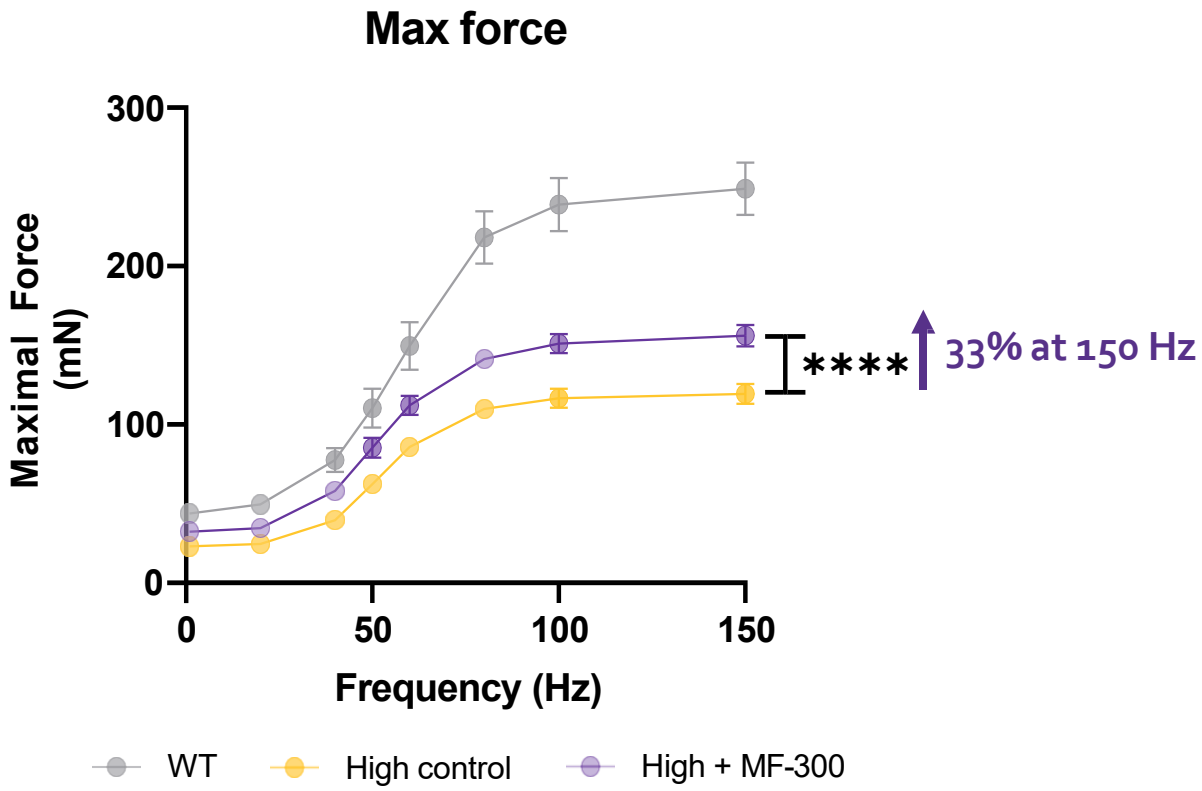
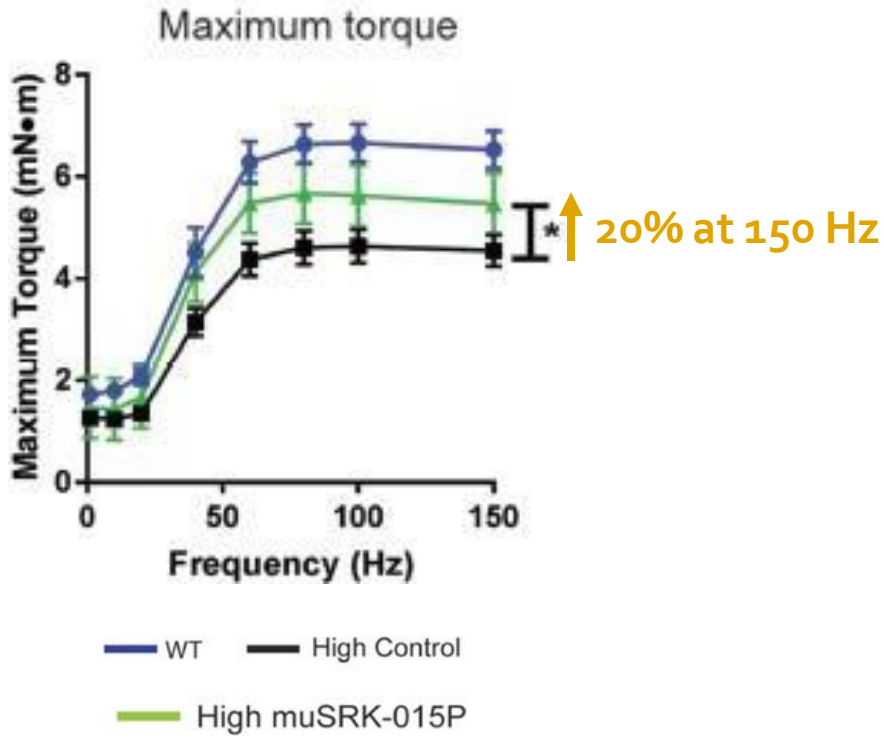
MF-300 in SMNΔ7 High/High Male mice



mSRK-015P in mouse Δ7 High/High Male and female mice



Force = Torque

MYOLOGICA

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

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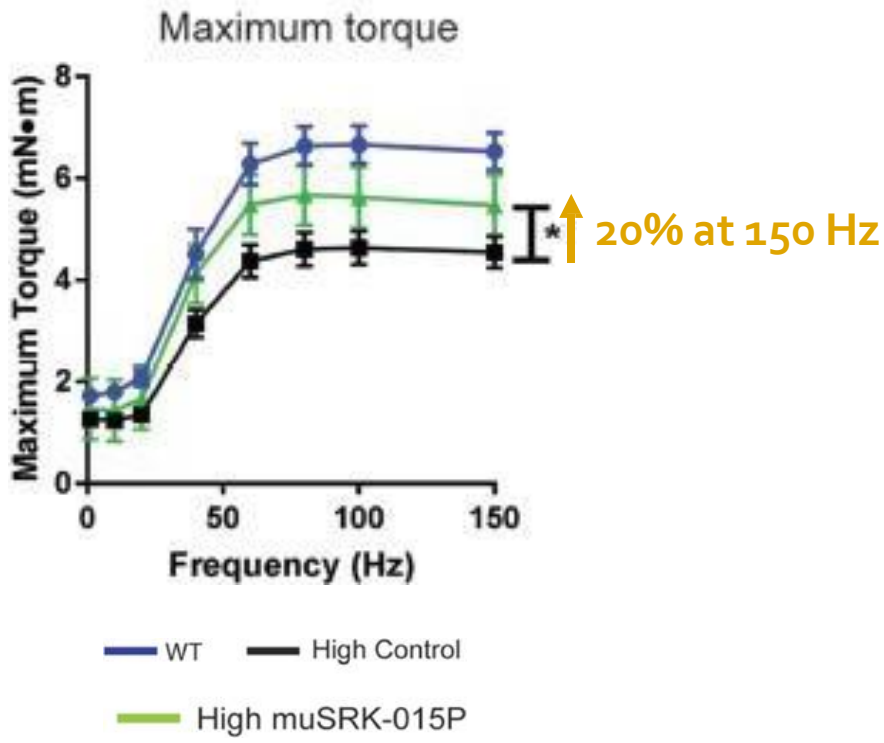
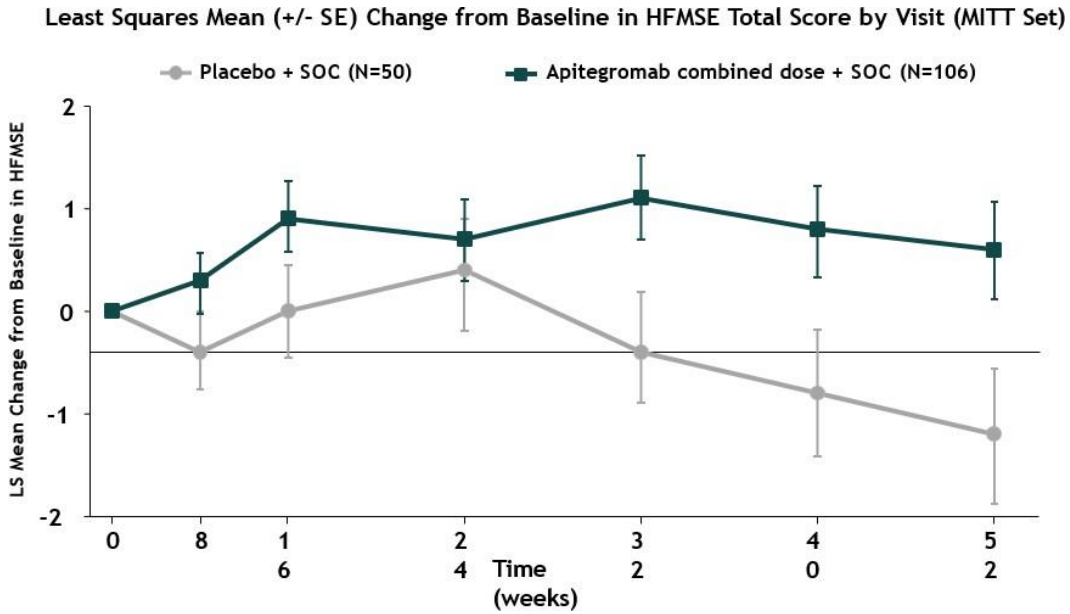
Demonstrates that a 20% increase in isometric plantar flexor force in mice translates to clinical benefit

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

The Aged Mouse is a Model to Study MF-300's Effect on Muscle Quality

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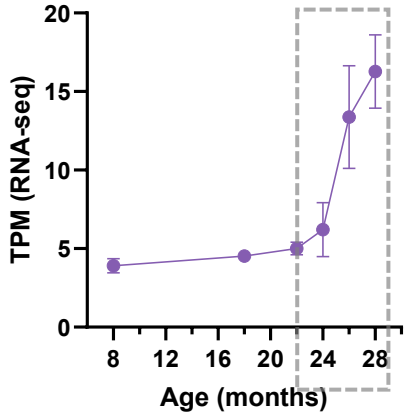
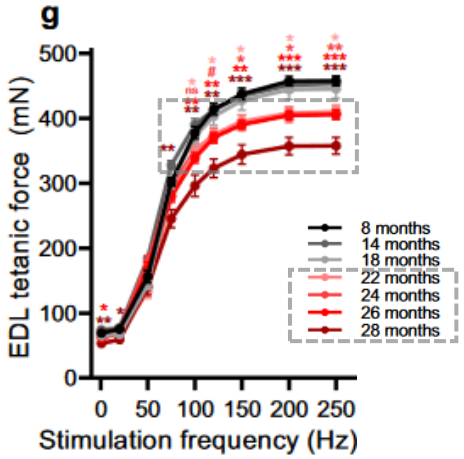
15-PGDH gene expression Elevated in aged mouse muscle

Muscle 15-PGDH gene expression (*Hpgd*) increases during aging[1]



- C57BL/6JRj, male
- Gastrocnemius

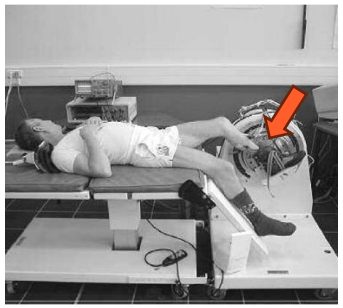
Muscle strength declines during window of elevated *Hpgd*[2]

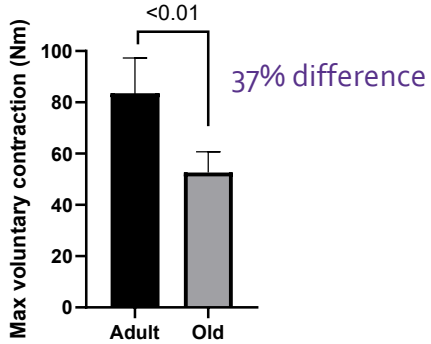


[1] https://sarcoatlas.scicore.unibas.ch/ GSE145480 , [2] Borsch et al., *Com Bio* 2021

Modeling age-induced muscle weakness with isometric plantar flexion in mice

Maximal voluntary contraction



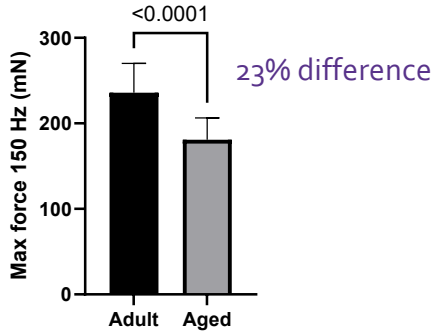


37% difference

Male
Adult (N=12): 19-24 y.o.
Old (N=11): 61-74 y.o.

Graph data and image:
Ochala et al., *Exp Ger*, 2004

Electrical nerve-evoked contraction



23% difference

Male (C57Bl/6J)
Adult (N=15): 12 m.o.
Aged (N=18): 23 m.o.

Mouse image:
https://aurorascientific.com/