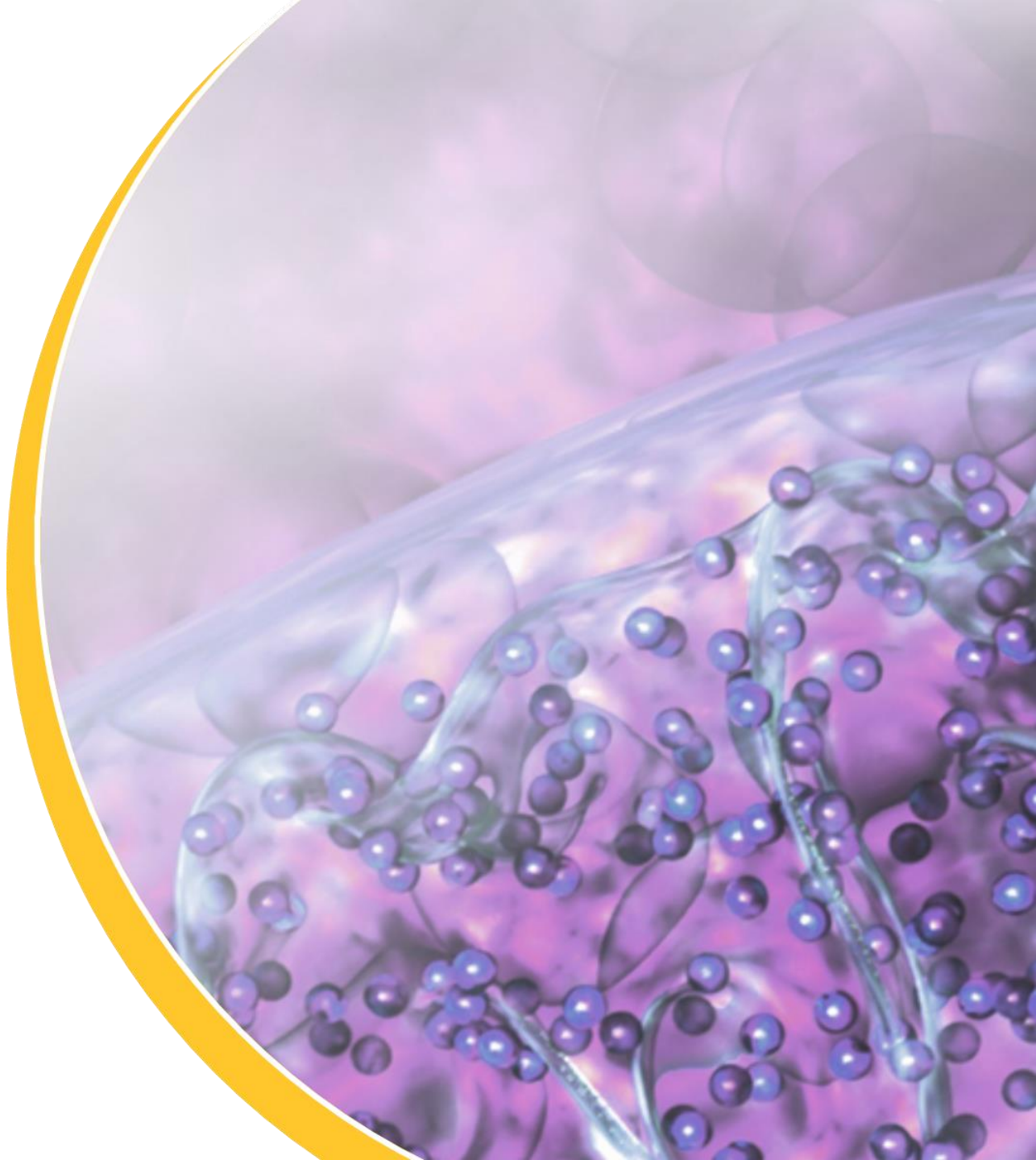
Epirium Bio

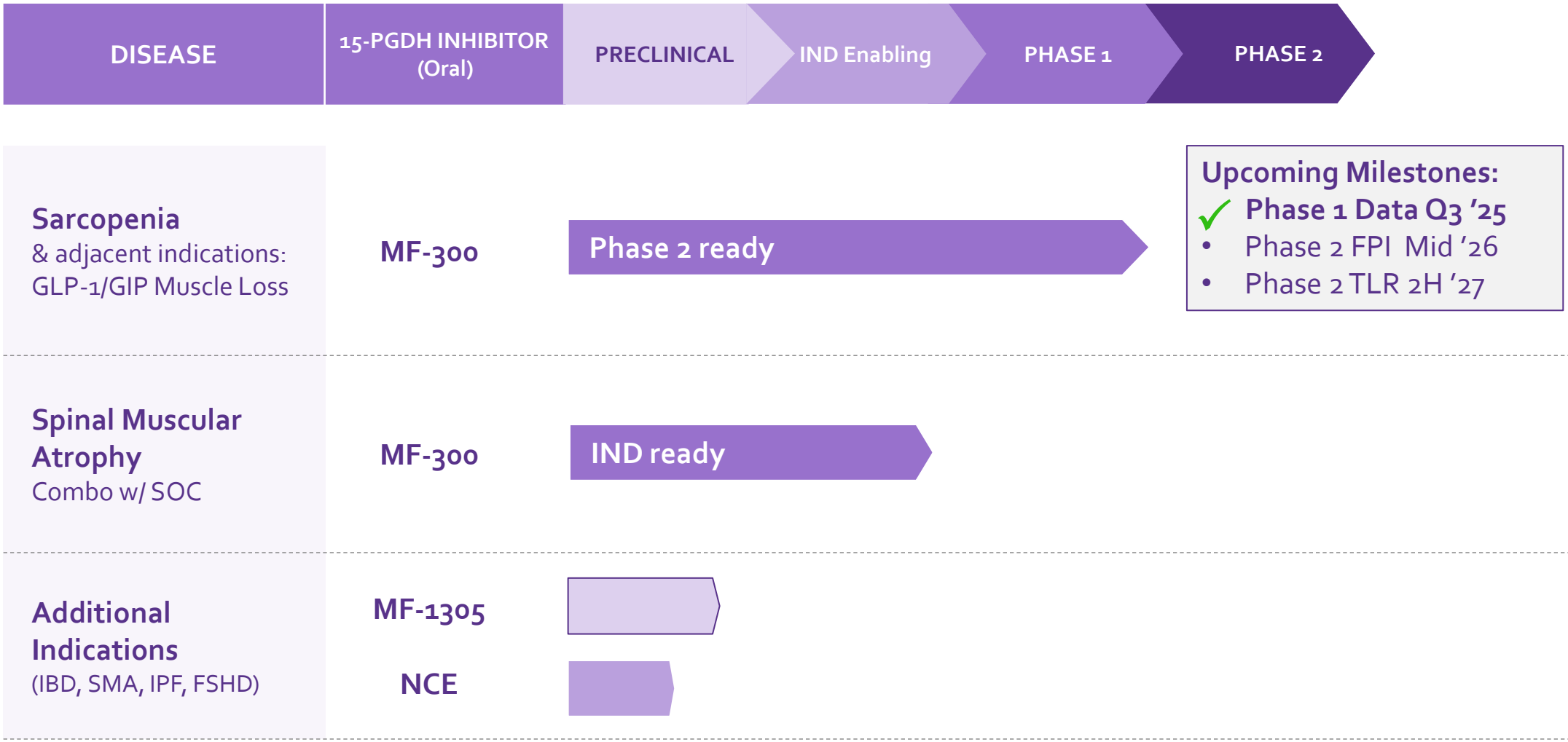
## Novel Oral 15-PGDH Therapy Platform: Improving Muscle Strength to Treat Sarcopenia and Neuromuscular Disease

- MF-300 "First-in-Class" Oral Sarcopenia Therapy
- Additional Indication Opportunities:
  - Sarcopenic Obesity, SMA and IBD



# Development Status of 15-PGDH Inhibitor Program

- Epirium is developing oral small-molecule 15-PGDH inhibitors to harness PGE2-mediated tissue repair pathways in areas of unmet medical need: including sarcopenia, rare neuromuscular diseases, IBD and lung fibrosis (IPF)



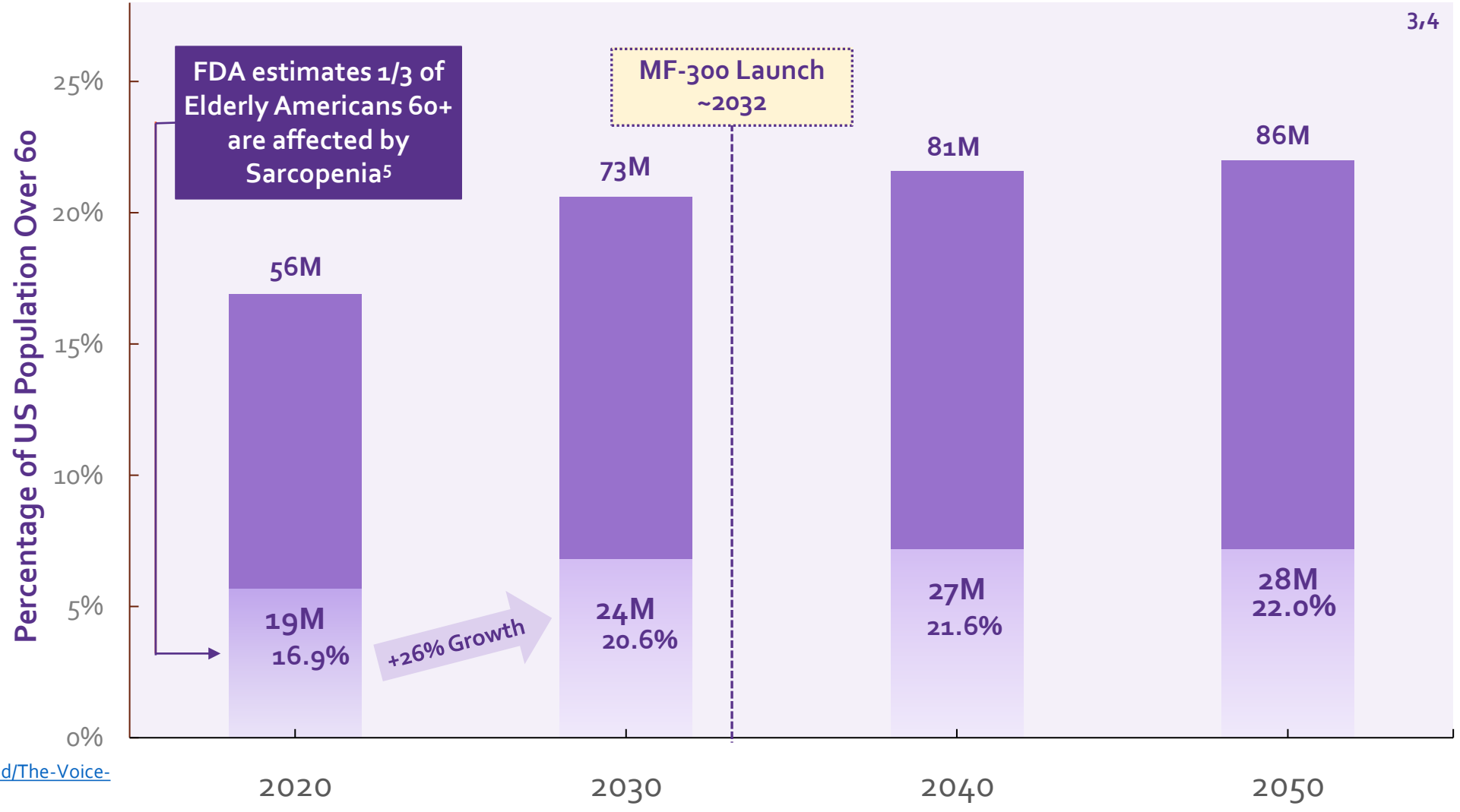
# Sarcopenia: Large and Growing Unmet Medical Need w/ No FDA Approved Therapy

## Current U.S. Healthcare Sarcopenia Spending Estimated >$40 Billion Annually[1]

**Dependence**
~7 million seniors "at-risk" of losing independence

**Falls**
Increased Morbidity & Mortality[2]

**Mortality**
Increased risk of death[2]




U.S. Population est. 331M


1. Goates S, et al. J Frailty Aging. 2019.
2. www.agingresearch.org. Sarcopenia Facts and Figures
3. Burns ER, J Safety Res. 2016.
4. Papadopoulou SK. Nutrients. 2020.
5. https://www.fda.gov/files/about%20fda/published/The-Voice-of-the-Patient--Sarcopenia.pdf

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Epirium Scientific Platform:

- Mechanism of Action (MOA)
- Preclinical Muscle Force & Biomarker Results

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

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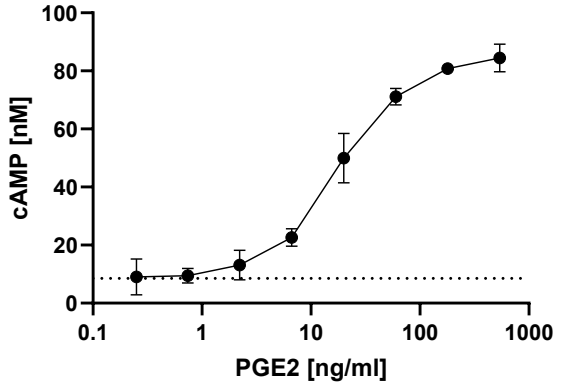
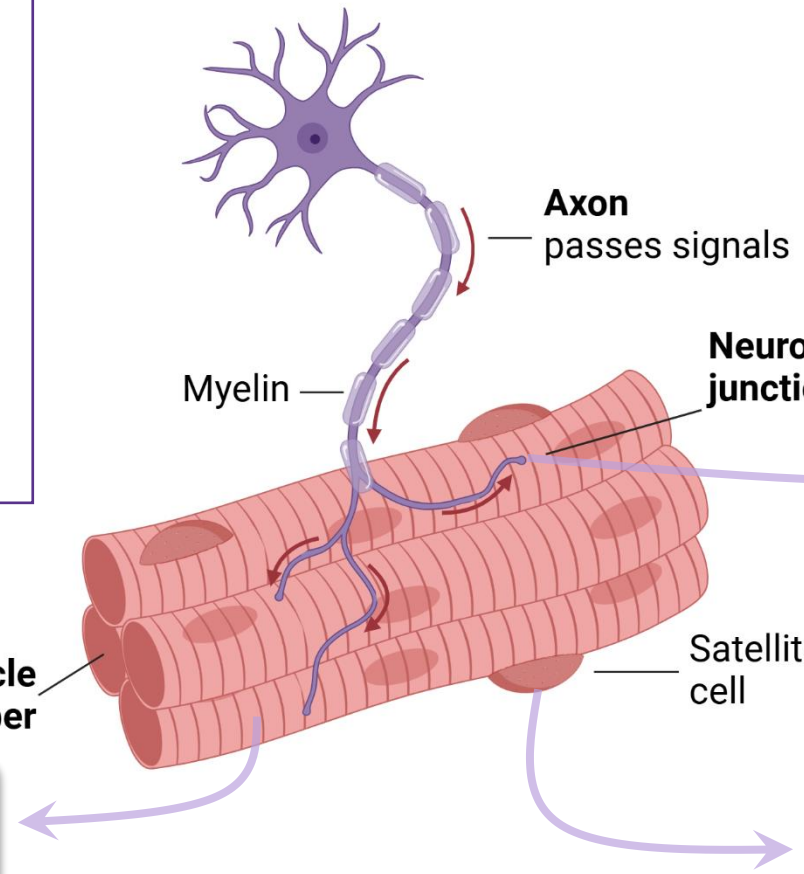
**PGE2 increases cAMP in primary human myocytes**




15-PGDH ⊣ PGE2 → EP4 → cAMP

*Epirium cell-based assay*




## *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 that Reduces PGE2 Levels, is Upregulated in Aged Muscle

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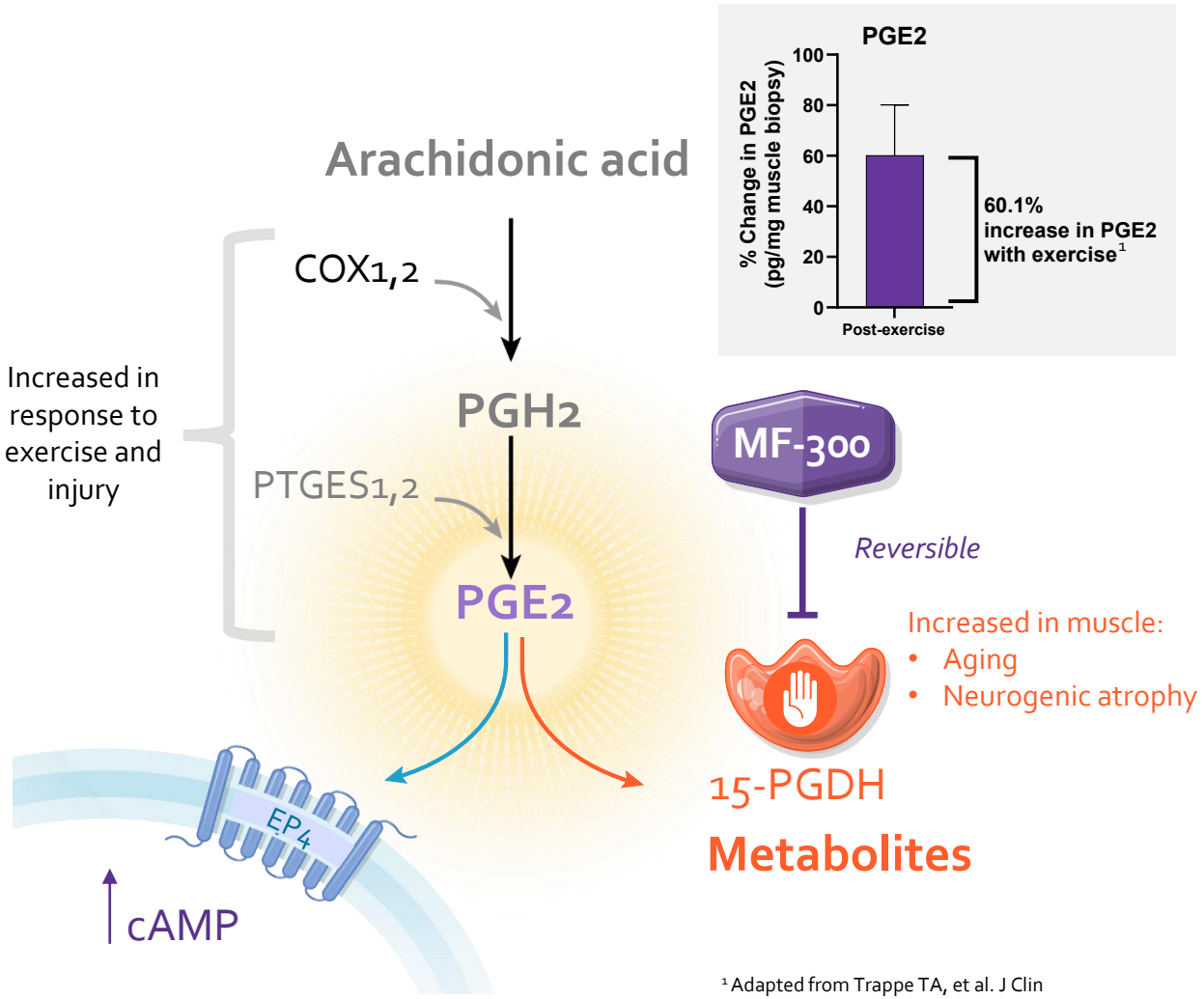
## 15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2

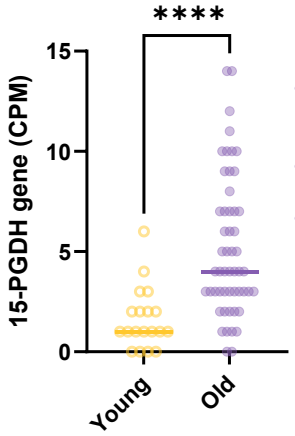




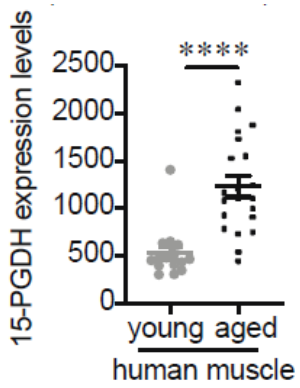


[1] Adapted from Trappe TA, et al. J Clin Endocrinol Metab. 2001;86(10):5067-5070

## 15-PGDH gene expression Elevated in aged human muscle[2,3]

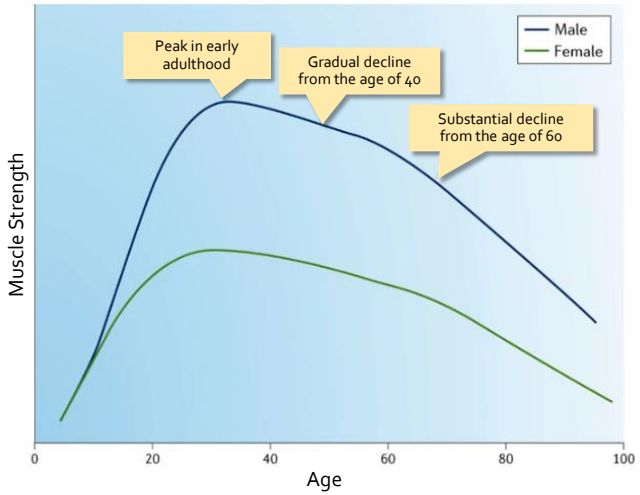



- Vastus lateralis (women and men)
- Young, N = 19 (**25±3 y.o.**)
- Older, N = 29 (**78±6 y.o.**)




- 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[4]



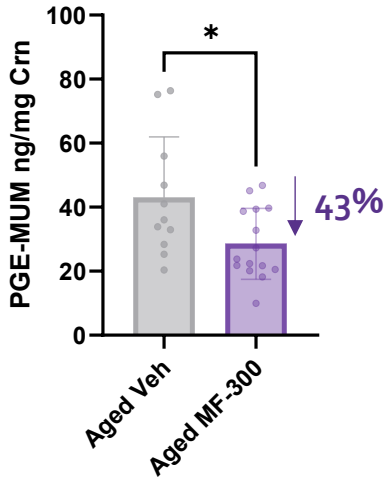

[2]GEO167186, [3]Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), [4]Dennison et al., *Nat Rev Rheum* 2017

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

## Preclinical Sarcopenia Studies

**MF-300 target dose**
**Increased muscle force and reduced PGE2 Metabolite in aged mice**

Study 1

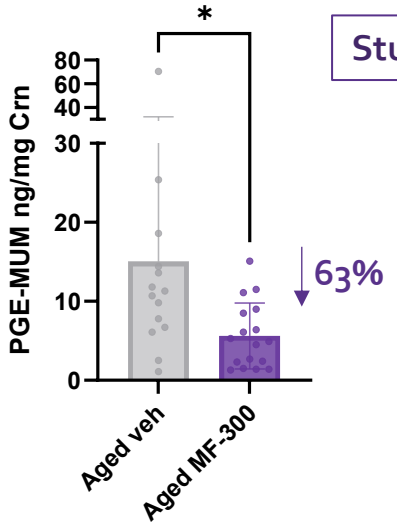


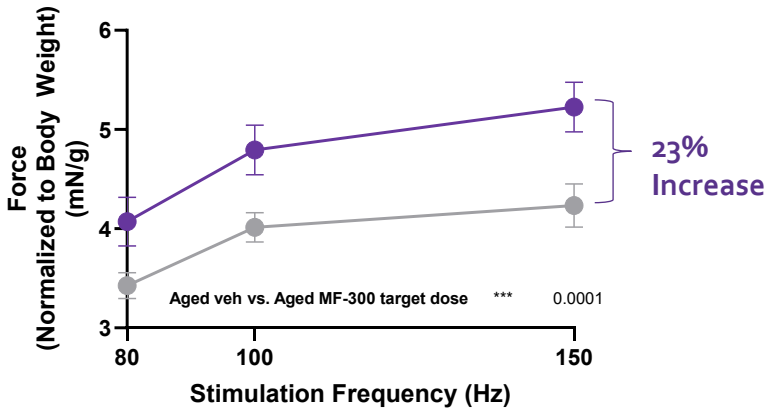

Vehicle
MF-300 target dose mg/kg

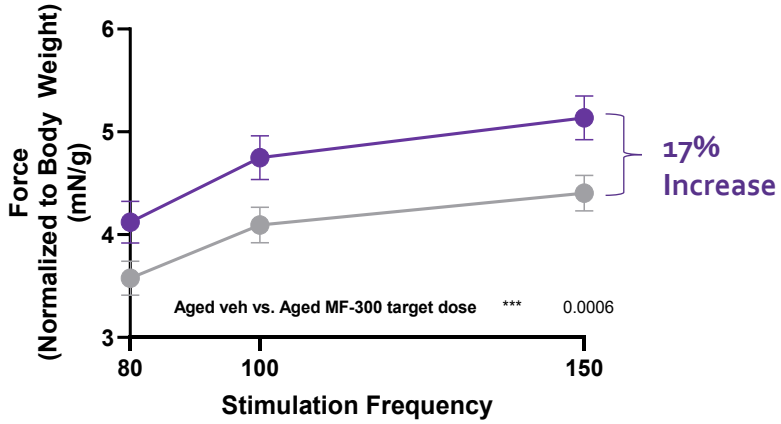
**PGE-MUM**
↓ ~50% average

**Force**
↑ ~20% average

Study 2




## Target Engagement Biomarker

- ~50% reduction in PGE-MUM is correlated with
- ~20% improvement in muscle force

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# MF-300 Sarcopenia Clinical Development:

- MF-300 Phase 1 Study Results
- MF-300 Phase 2 Study Overview

# Phase 1 Proof of Mechanism Study

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

**Populations:** Adult healthy volunteers ≥ 18 - ≤ 65 years of age & Healthy elderly cohort >65 - ≤75 years of age

**Doses:** SAD explored 5 doses ranging from 75mg to 800mg; MAD explored 3 doses of 75mg, 125mg, and 200mg

## Part 1a SAD

- N=8 per cohort (2 pbo, 6 MF-300)
- Doses: 75, 125, 250, 500, & 800mg

Single Ascending Dose
5 non-elderly cohorts, 1 elderly cohort

## Part 1b Food Effect

- N=12 (all MF-300)
- 500mg 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
- Doses: 75mg, 125mg, 200mg

Multiple Ascending Dose
3 non-elderly cohorts & 1 Elderly cohort

# Phase 1 Clinical Success Criteria to Enable Phase 2

- **All predefined Phase 1 success criteria across Safety, PK, and PD were achieved**
- **Enabling advancement into Phase 2**

## Safety

- ✓ Safe and well-tolerated
- ✓ No unexpected or dose-limiting findings
- ✓ Majority of adverse events mild and self-limiting
- ✓ No discontinuations due to adverse events

## PK

- ✓ Exposure increases predictably with dose
- ✓ Half-life supports once daily dosing
- ✓ Human PK exposures aligned with preclinical efficacy targets

## PD

- ✓ Evidence of target engagement (PGE2 metabolite) w/ substantial proportion of subjects achieving ≥50% reduction in PGE-MUM
- ✓ Evidence of mechanism-increased PGE2 levels
- ✓ Clear dose/response relationship defining therapeutic range, supportive of Phase 2 dose selection

# MF-300 Phase 1: Safe and Well-tolerated Across a Broad Range of Doses

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## MF-300's Safety Profile Supportive of Continued Development

**Safe and well tolerated across the evaluated dose ranges**

- No deaths, SAEs, or discontinuations due to AEs
- Maximally tolerated dose not identified up to 800 mg (therapeutic range 75-200mg)

**Adverse Events: No dose-limiting Toxicities**

- No maximally tolerated dose identified, majority of adverse events mild, resolved with intervention. No dose-response in frequency or severity of AEs.
- With repeat dosing (MAD): No difference in overall AE incidence between MF-300 and placebo.
- **Most common AE:** Mild diarrhea: 30% overall incidence in SAD, single event in MAD; transient (resolving w/in 1-2 days)

**Laboratory / Vital Signs / ECGs: No clinically meaningful trends in labs, vital signs, or ECGs**

- Fasting glucose remained stable
- Some fluctuations in blood pressure and heart rate consistent with placebo
- No QTc prolongation or hemodynamic concerns

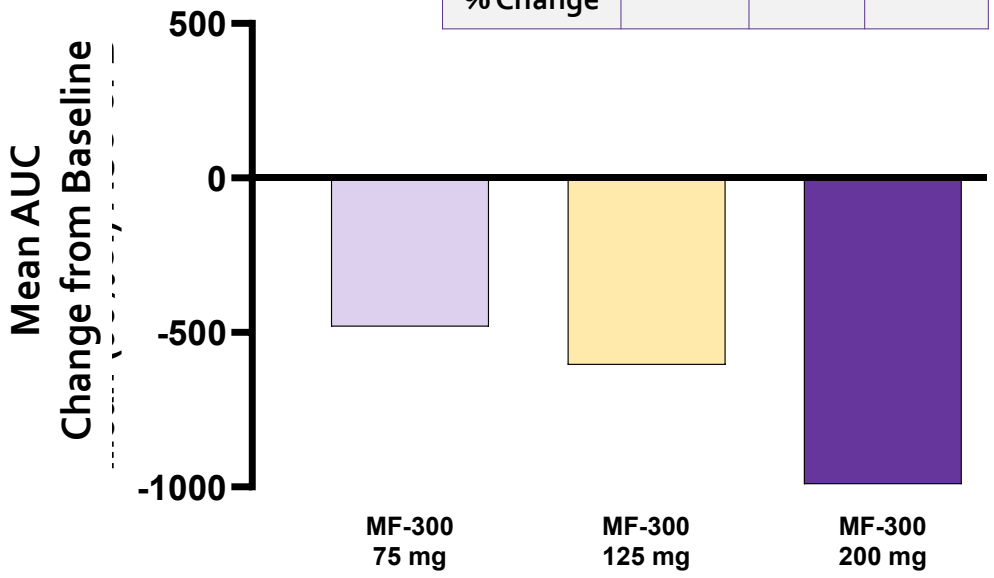
***No additional monitoring required beyond standard Phase 2 assessment***

# Increased PGE2 Levels with MF-300 Demonstrates Proof of Mechanism

- Reductions in PGE-MUM are consistent with those associated with ~20% improvement in muscle force in sarcopenia mice model
- Increases in PGE2 are consistent with those following eccentric exercise in humans

## Placebo-adjusted PGE-MUM Change from Baseline (95% CI)

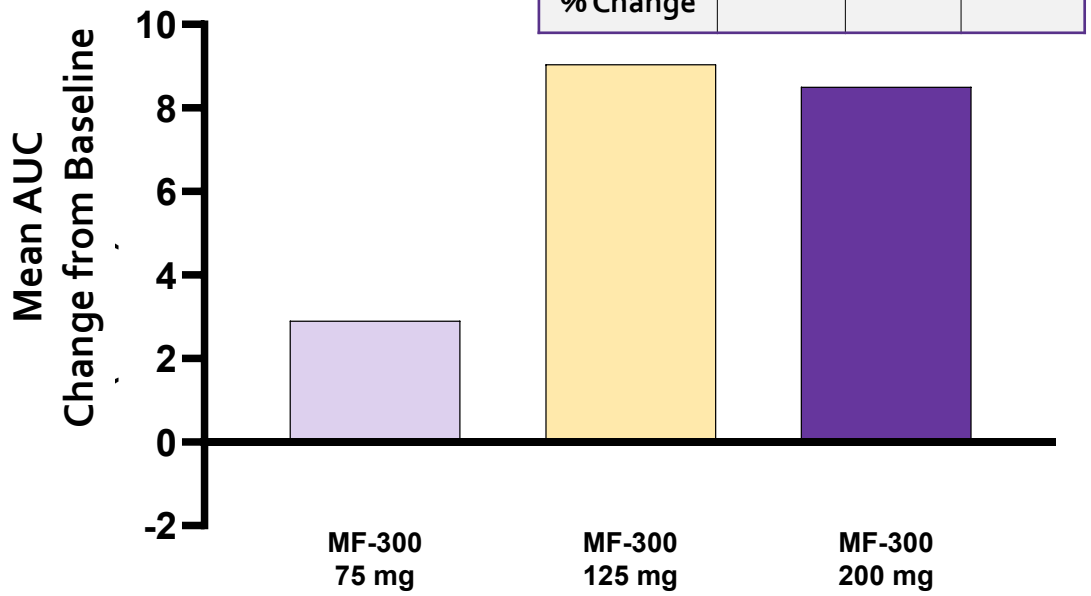
| MF-300 (mg) | 75 | 125 | 200 |
|---|---|---|---|
| Placebo Adj. % Change | -64% | -64% | -83%* |




*p<0.05 versus placebo (95% CI does not include 0)

## Placebo-adjusted PGE2 Change from Baseline (95% CI)

| MF-300 (mg) | 75 | 125 | 200 |
|---|---|---|---|
| Placebo Adj. % Change | +77% | +116% | +128% |




Note: Two outlier subjects in the 75 mg group, with markedly greater PGE2 responses due to low baseline values, were excluded from analysis, including the two subjects = 614% increase in MF-300 75 mg dose group.

# MF-300 Drives Desired Biologic Response: ↓ PGE-MUM & ↑ $PGE_2$

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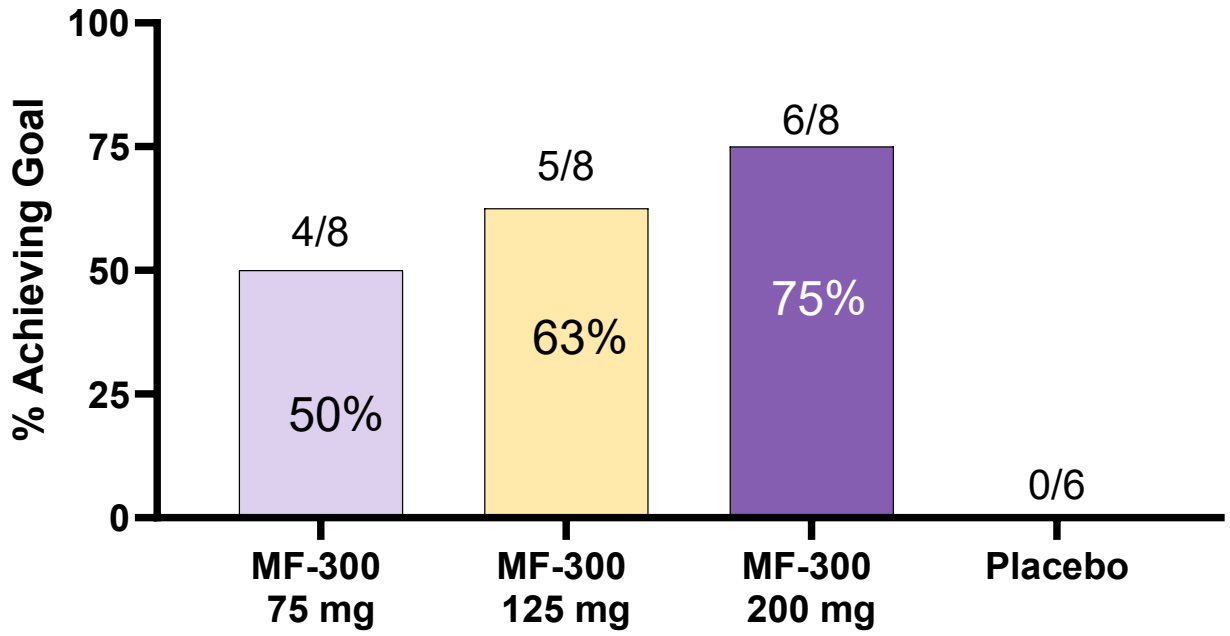
## Proportion of Subjects Achieving Targeted % decrease in PGE-MUM & 60% Increase in PGE2




**Rationale for targets:**

- ~Targeted % reduction in PGE-MUM is associated with ~20% improvement in muscle force
- ~60% increase in muscle following eccentric exercise in humans[1]

Subjects were counted only once with their maximum improvement at any timepoint (Day 1-5).

[1]Trappe et al., *J Clin Endo Met* 2001

# Phase 2: 24-week Randomized, Double-blind, Placebo-controlled Study (N=200)

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

- Low grip strength (<35.5 kg for men, <20 kg for women)

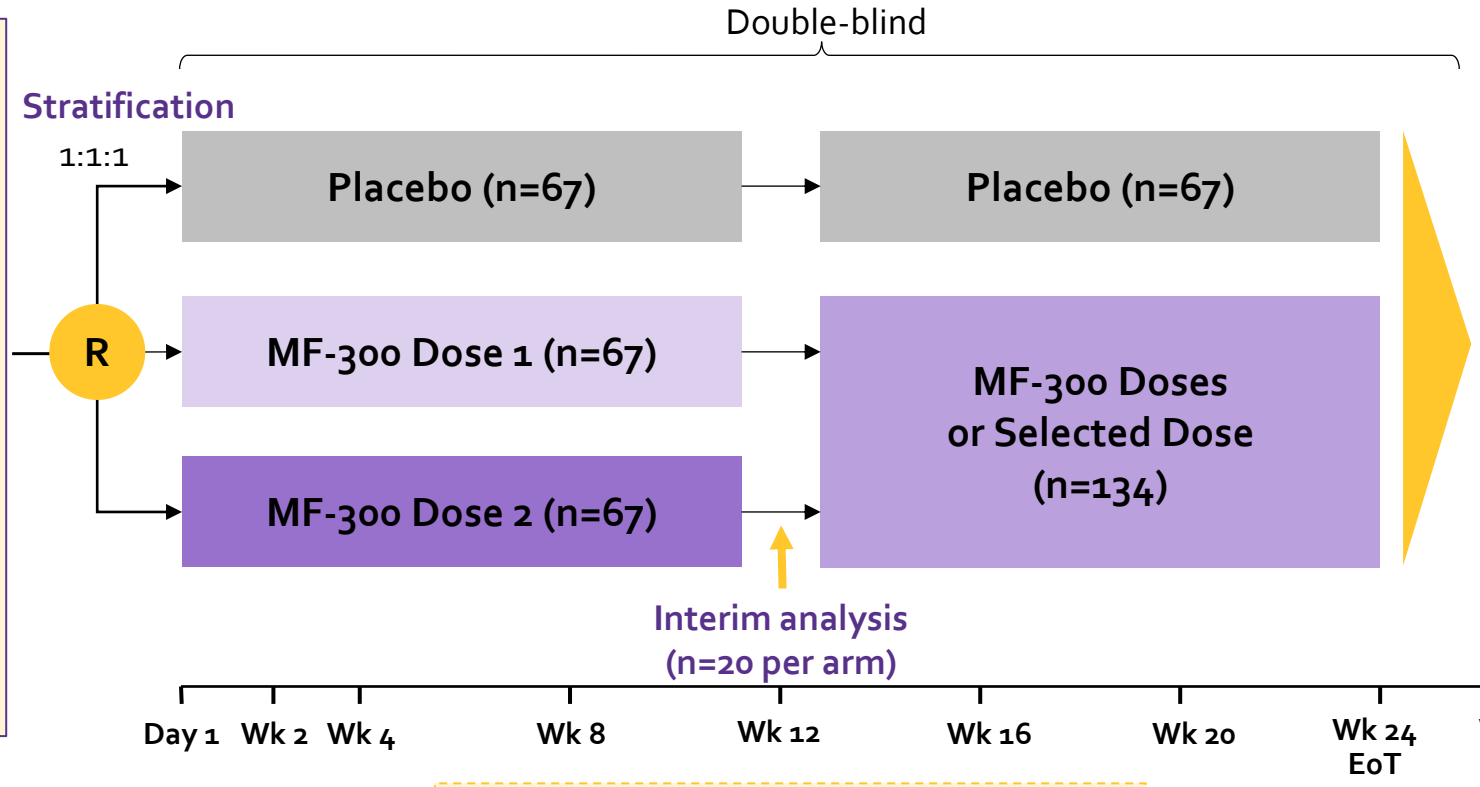
&

- Slowness (walking speed <0.8 m/s)

**SPPB Score 4 – 8**

**5x CST (13.7 – 60 sec)**[2]

- Enrich for Poor Performance (>16.7 sec)




**Primary Endpoint**:

- 5x Chair Stand Test

**Key secondary endpoints**:

- Knee extension strength
- 4-meter gait speed test
- 6-min walk test
- SPPB
- Hand grip strength
- Fall Risk
- PROs

**Screening (≤4 weeks)**

**Interim Analysis based on unblinded efficacy and safety data by DMC**

*The study provides **~80% power** to detect a **15% difference** between the active and placebo groups

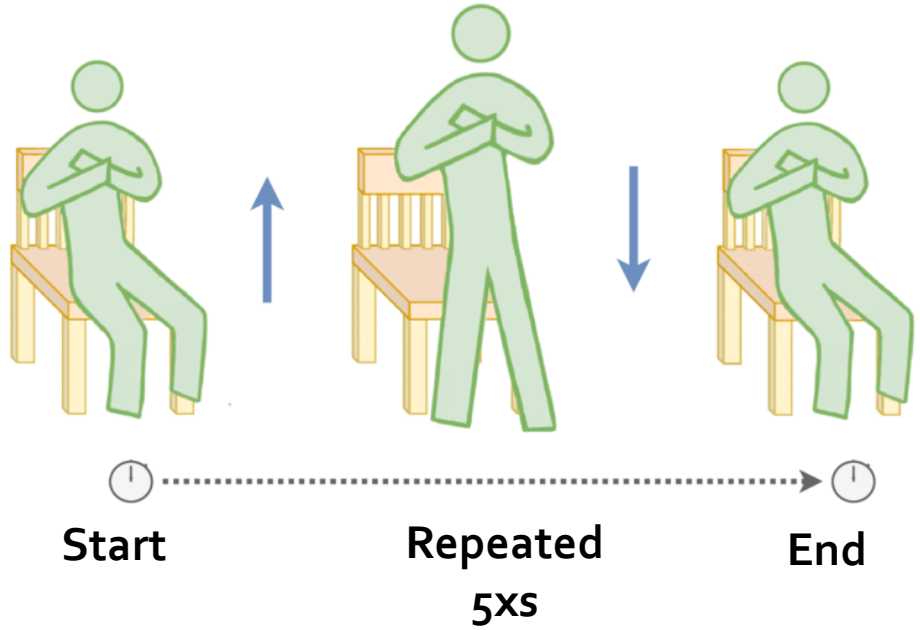
DMC=Data Monitoring Committee; EoT=end of treatment; EoS=end of study; R=randomization; SDOC=Sarcopenia Definitions and Outcomes Consortium; SPPB=Short Physical Performance Battery; Wk=week; yo=years old

1. Bhasin S, et al. J Gerontol A Biol Sci Med Sci. 2023;78:S86–S93.

# Rationale for the 5x Chair Stand Test as the Primary Endpoint

- **Accepted proxy measure of lower limb power and strength**
  - Endorsed by World Health Organization (WHO) ICOPE[1] & EWGSOP2[2]
  - Core component of SPPB[3]
- **Strong predictor of clinical outcomes**
  - Activities of daily living
  - **Fall Risk: Measured in Phase 2**
  - All-Cause Mortality
- **Assesses Locomotor Capacity, a key domain of Intrinsic Capacity**
- **Loss of 1 second (~10%) per year is considered clinically significant**

5xs Chair Stand Test




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. SPPB = Short Physical Performance Battery

# Building Leadership in Sarcopenia w/ Key Clinical Milestones & Activities

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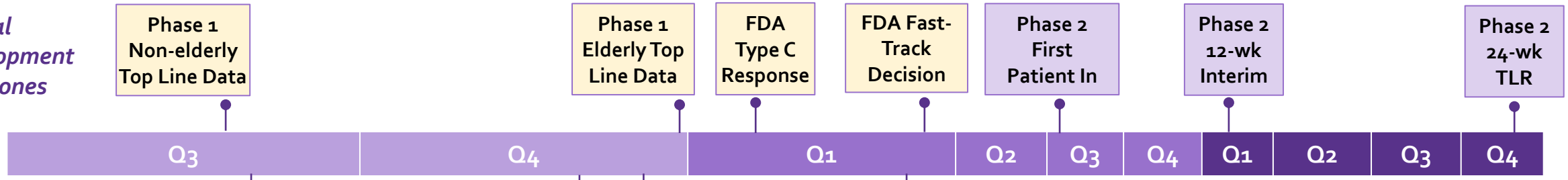
*Clinical Development Milestones*




*Data Presentations*

**FDA Sponsored Sarcopenia PRO & PerfOs Qualification Study**

**MF-300:** Late-breaker Phase 1 Results
Gerontological Society of America (GSA) Meeting
Boston, MA
**Nov 12 – Nov 15,2025**

**Epirium Presentation:** Phase 1 Results & Clinical Plan Overview
Society of Sarcopenia, Cachexia & Wasting Disorders (SCWD) Conference
Regulatory Forum w/ Industry Trial Design (EMA, ex-FDA, Industry)
Rome, Italy
**Dec 11 – Dec 13,2025**

**MF-300:** Oral Presentation Biomarker Data & Phase 1 PD Results
Intrinsic Capacity, Frailty & Sarcopenia Research Conference (ICFSR)
Washington, DC
**Mar 10 – Mar 12, 2026**

# Financial Review

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

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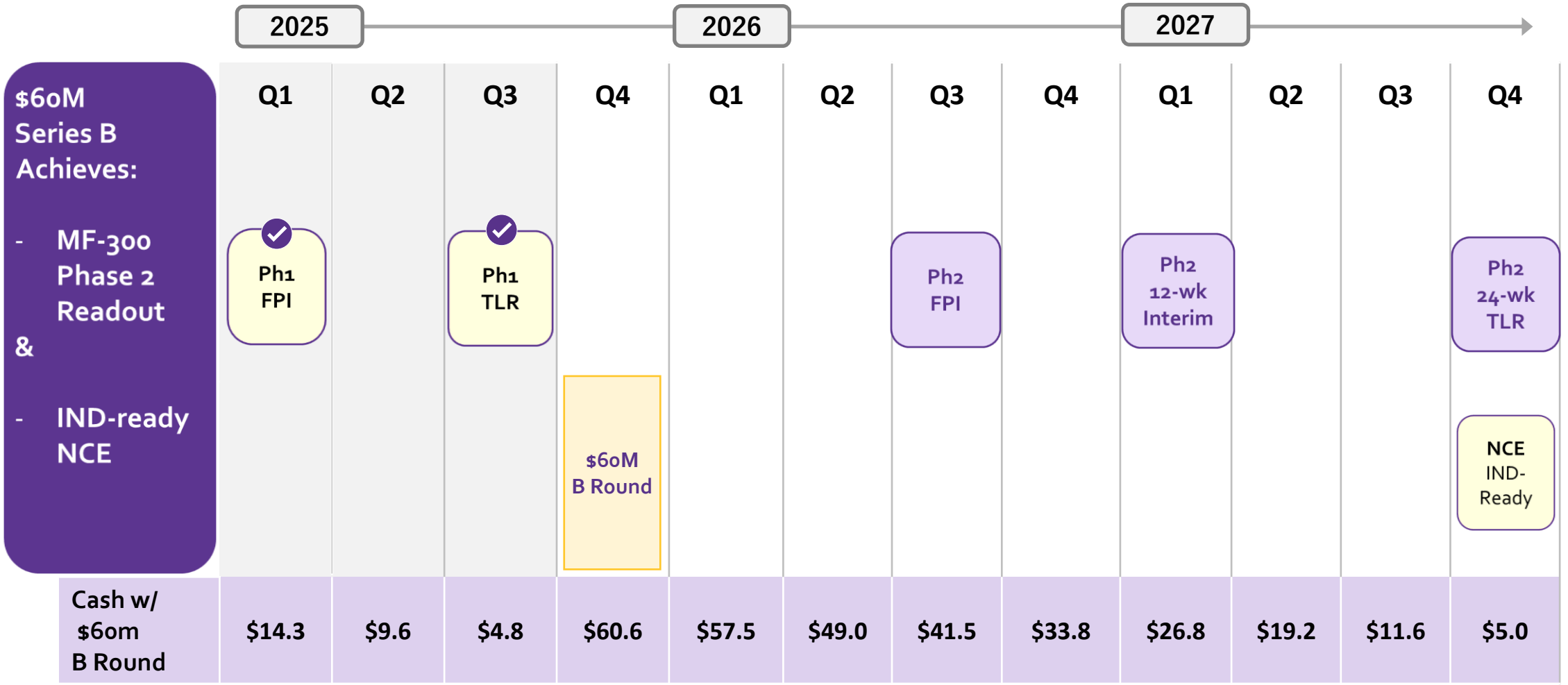


*Additional $20M ($80M raise) enables Phase 3 CMC commencement during Phase 2 (Interim look)*
*Bringing forward MF-300 Commercial Launch 6 months to 1H 2032*

# Appendix

- Team
- SMA Delta7 study results

# 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, 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 MacConell, 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)

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

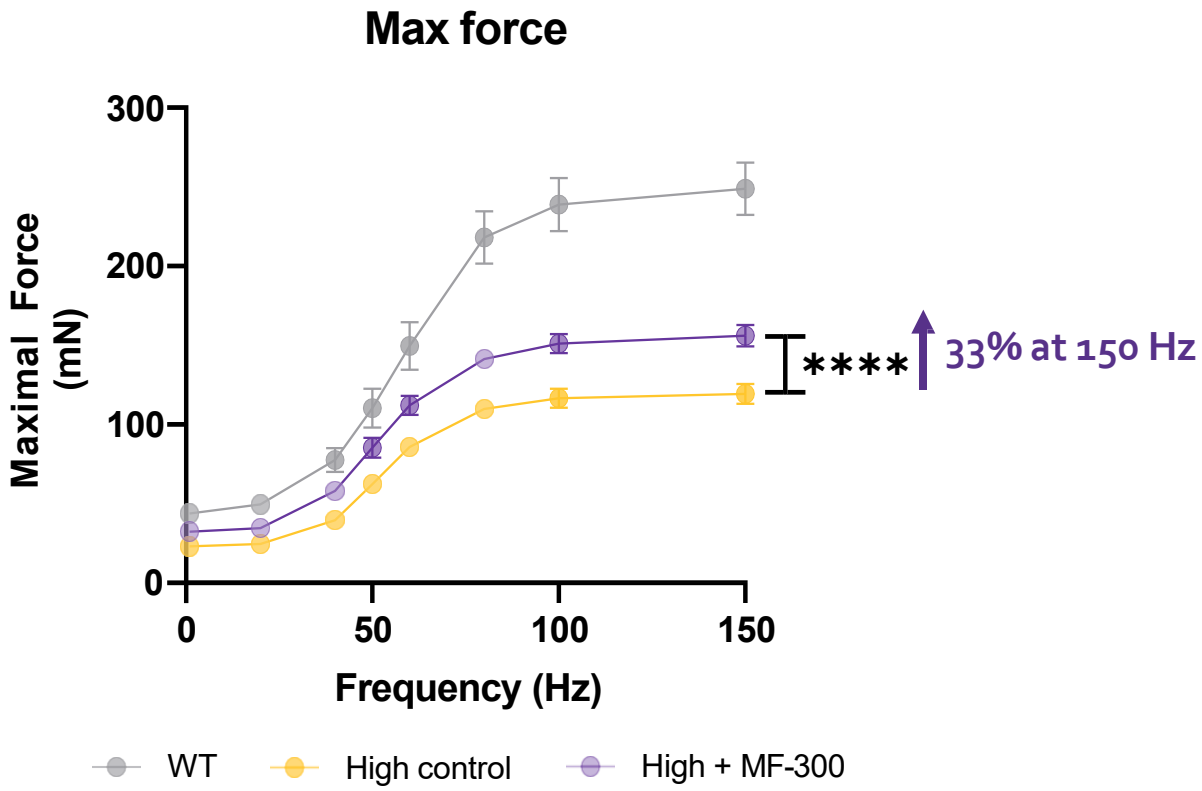
Published over 200 per-reviewed papers and 8,000 citations

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

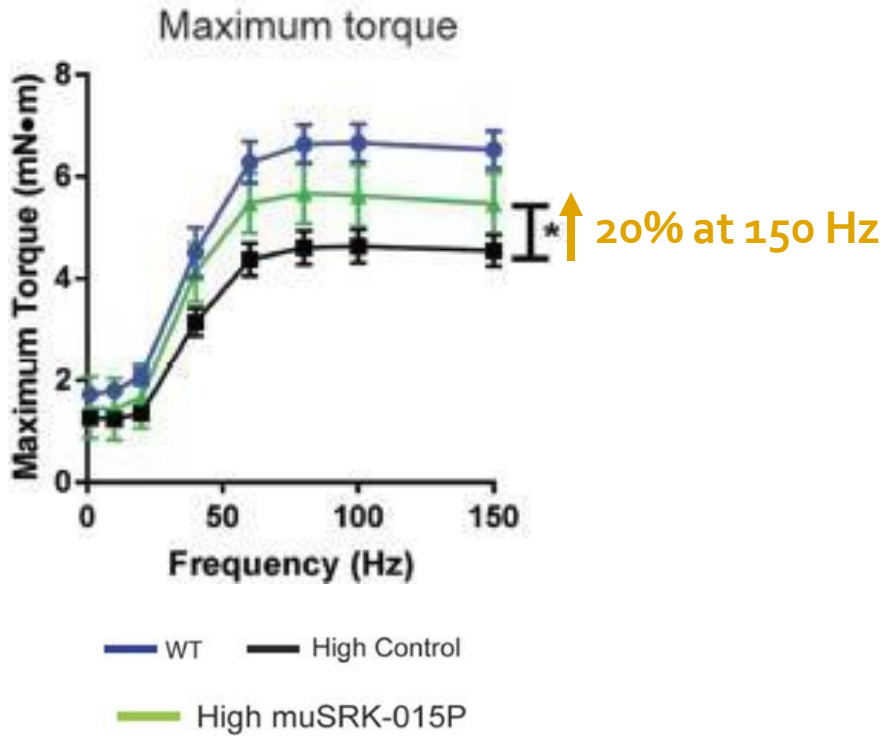
# MF-300 Attractive Profile in Translational SMA Model in Mice

Epirium Bio

## MF-300 in SMNΔ7 High/High Male mice




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




Force = Torque

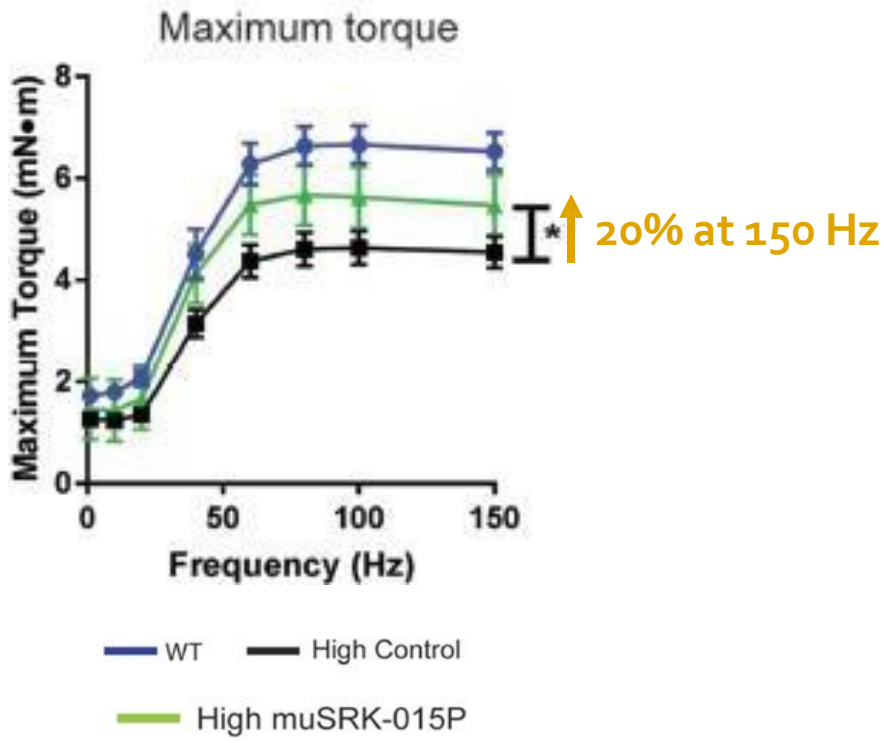
MYOLOGICA

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

Epirium Bio

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

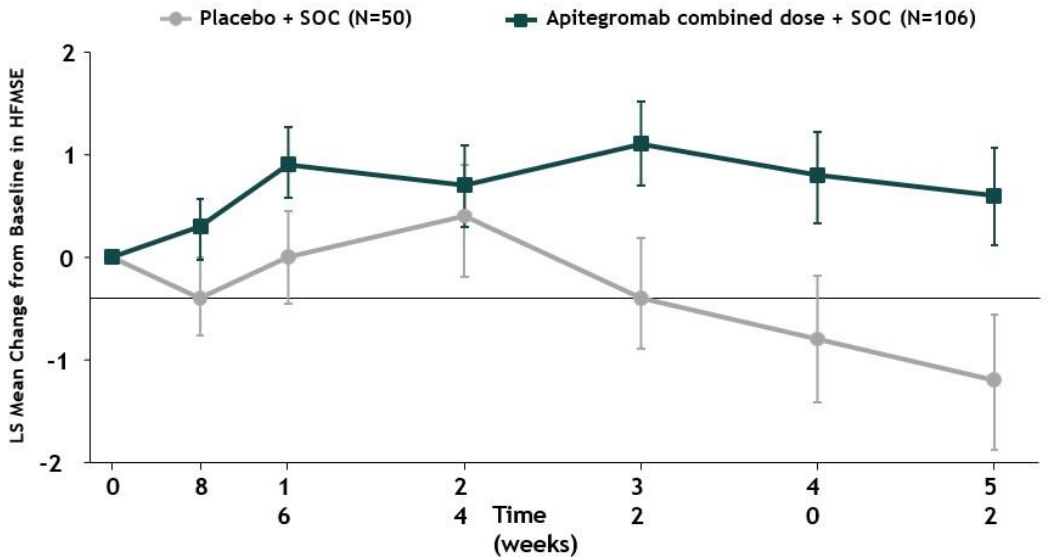
### mSRK-015P in mouse Δ7 High/High




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

### 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