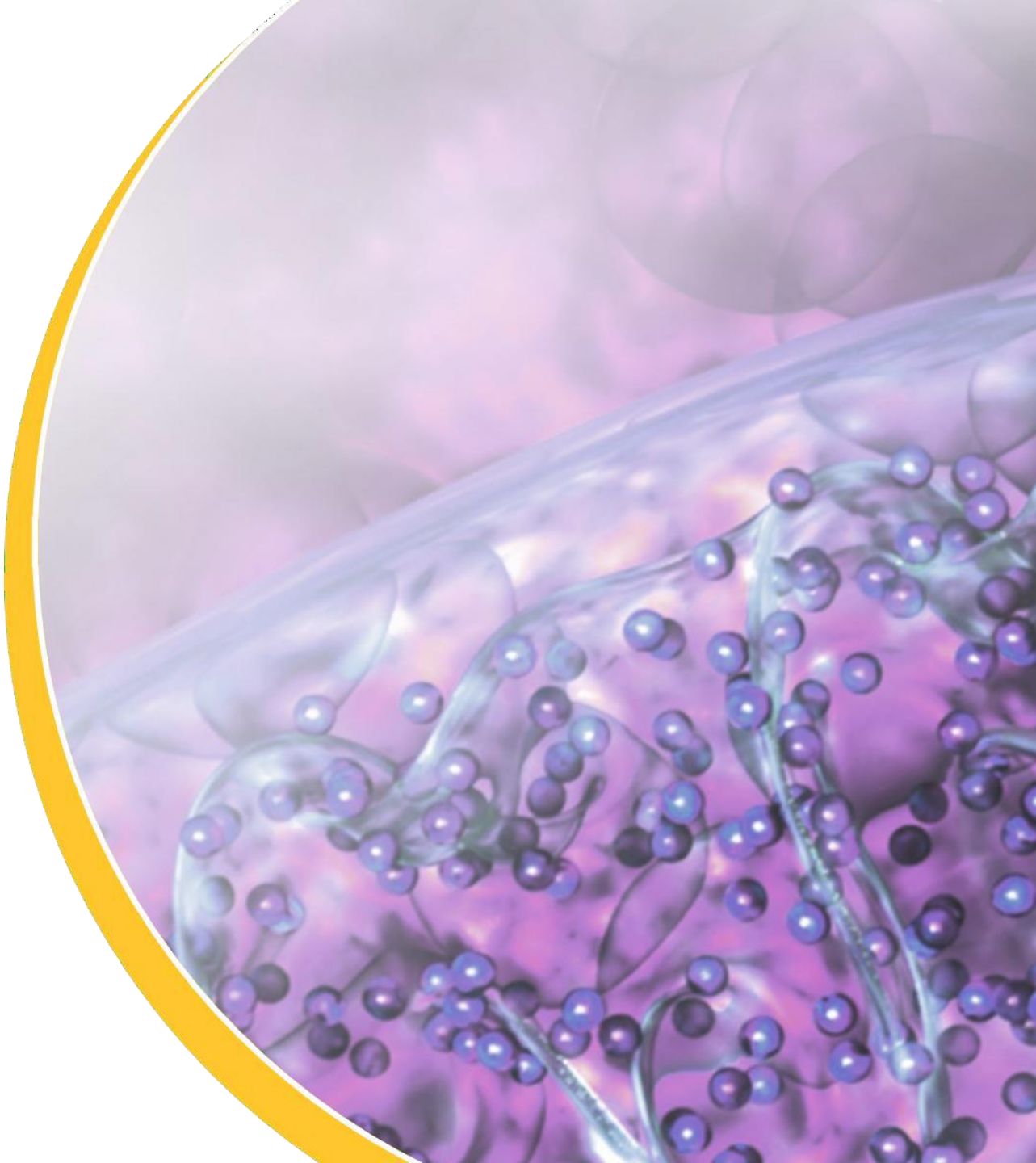
Epirium Bio

Oral 15-PGDH Inhibitor Platform:
Leveraging PGE2 Signaling To Treat Sarcopenia, Neuromuscular & Inflammatory Diseases (IBD):

- **MF-300, lead oral small molecule: Phase 2b Sarcopenia**



Experienced Team with a Demonstrated Track Record of Success

Epirium Leadership Team

Alex Casdin, CEO

30+ 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

Head Finance, Synthorx (acquired by Sanofi)

Corp. Controller & Head FP&A, Acadia Pharm.

Cadence Pharm. (acquired 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.
Head, Clinical Development

25 years drug development, primarily in metabolic and liver disease

Led multiple drug approvals including first in class forT2DM (GLP-1) and primary biliary cholangitis (PBC)

Collaborated with FDA to define approval pathways for disease areas without regulatory precedence, including PBC & MASH

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

Lois Lee, Pharm.D.
Clinical Development

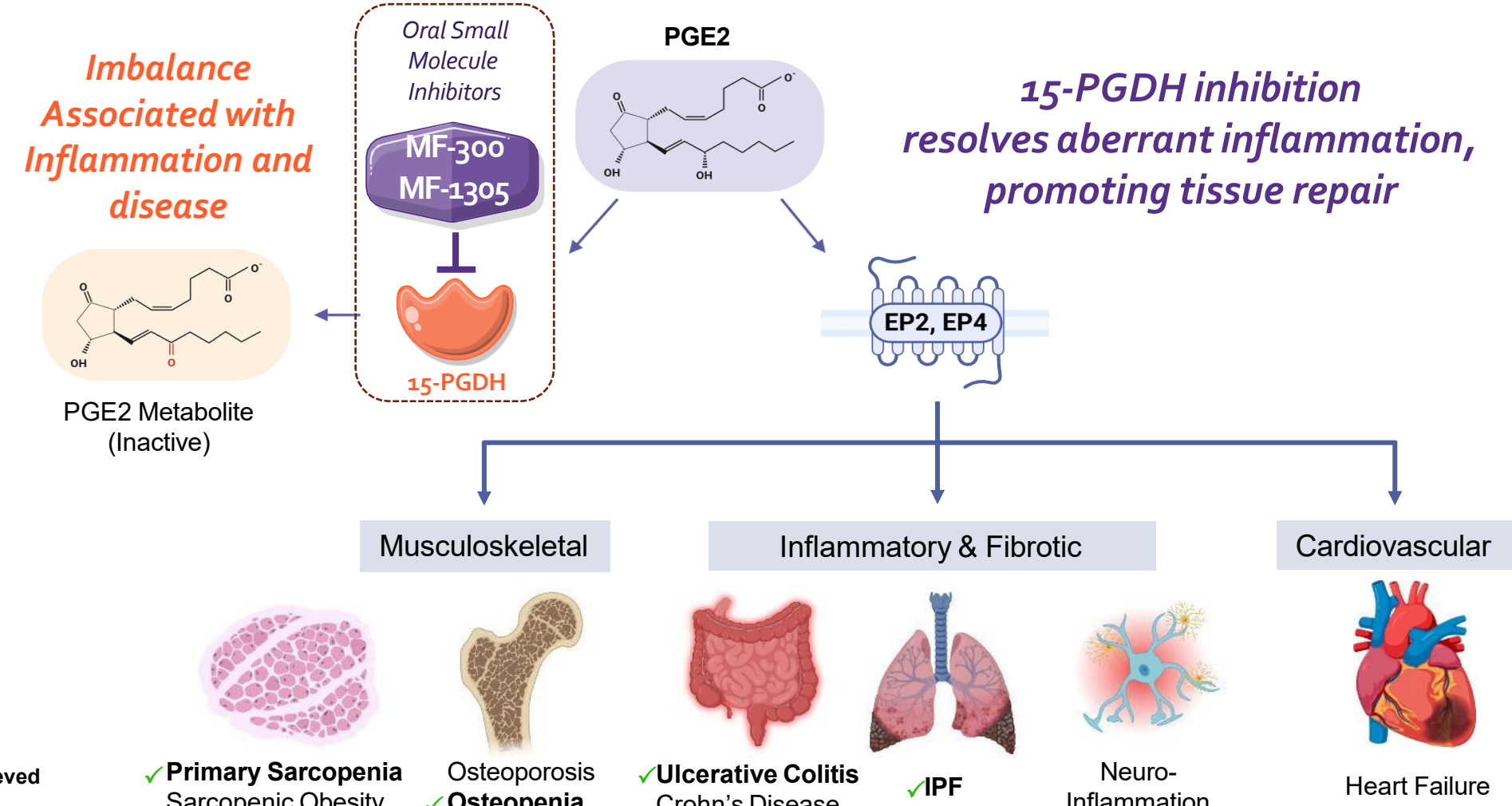
20+ years of industry experience leading early- and late-phase drug development across multiple TAs including liver, metabolic, and neurodegenerative diseases.

Extensive experience in collaborating with FDA and EMA on indications lacking regulatory precedent including MASH, MASH cirrhosis, and Alexander disease

Pipeline in a Mechanism: Unifying Biology Addressing Blockbuster Markets

Epirium Bio

Inhibiting 15-PGDH to leverage the potential of PGE_2 signaling in restoring tissue homeostasis: rebalancing inflammation, stimulating regeneration, reducing fibrosis



Epirium 15-PGDH Inhibitor Platform: "Pipeline in Mechanism"

Epirium Bio

Therapeutic Area		15-PGDH INHIBITOR (Oral)	PRECLINICAL / IND ENABLING / PHASE 1 / PHASE 2
Musculoskeletal	**Sarcopenia** *Potential label expansion: Sarcopenic obesity*	**MF-300**	**Phase 2b**
Musculoskeletal	**Osteoporosis***	**MF-300**	**IND ready**
Musculoskeletal	**Spinal Muscular Atrophy**	**MF-300**	**IND ready**
Inflammatory / Fibrotic	**IBD - Ulcerative Colitis, Crohn's Disease**	**MF-1305** **MF-300**	
Inflammatory / Fibrotic	**Idiopathic Pulmonary Fibrosis**	**MF-300**	

Preclinical Proof of Concept Achieved

Upcoming Milestones:

- ✓ **Phase 1 completed** Q4 '25
- ✓ **FDA End-of-phase 1** Q1 '26
- Fast track application Q2 '26
- Phase 2b FPI Mid '26
- Phase 2b TLR H2 '27

*Human proof of concept (bone biomarkers & bone mineral density) to be generated in Sarcopenia Phase 2b study

Epirium MF-300 Lead Program in Sarcopenia:

- Unmet Need
- Scientific Rationale
- Preclinical Muscle Force & Biomarker Results

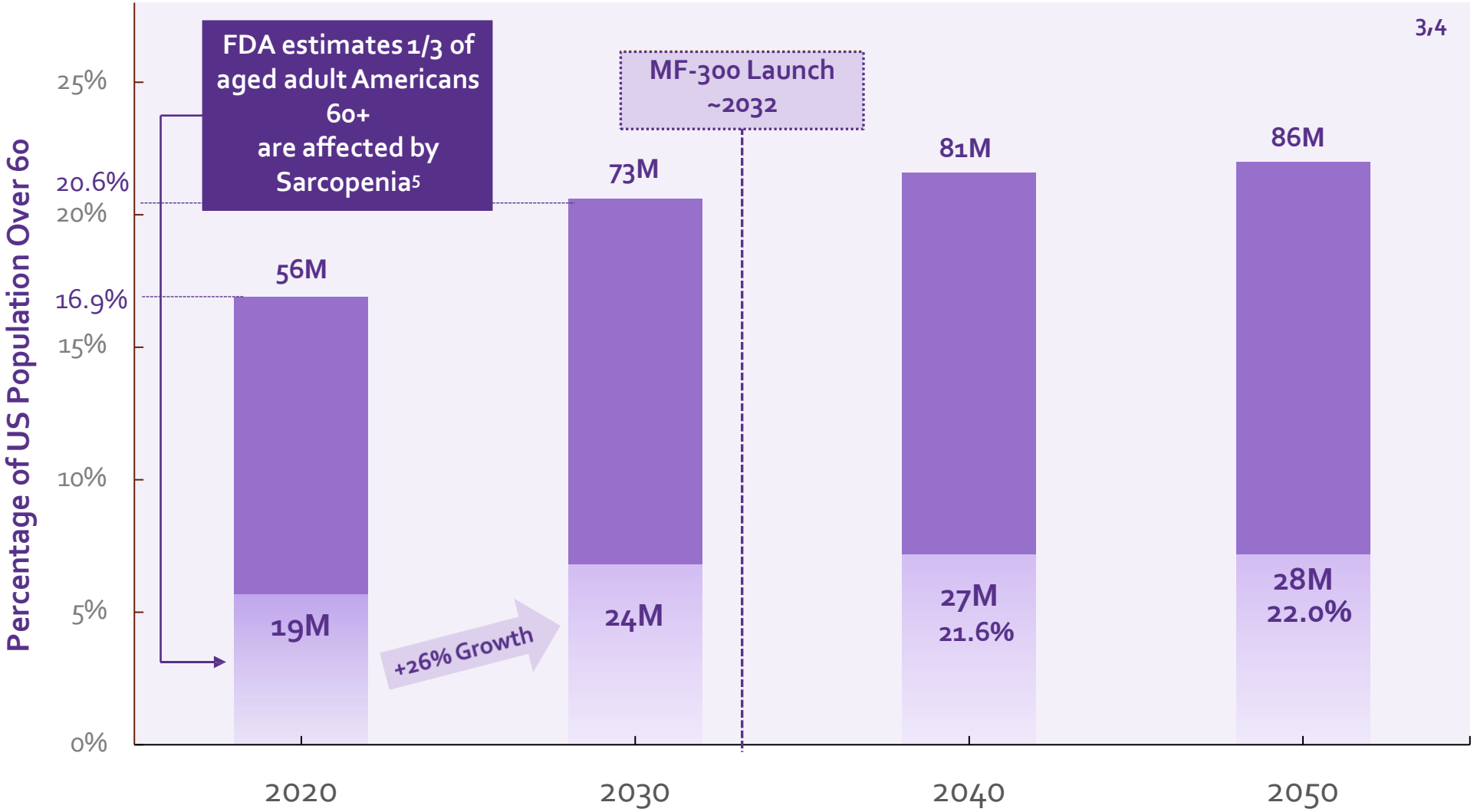
Sarcopenia: Large and Growing Unmet Medical Need w/ No FDA Approved Therapy

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

Dependence
Increased risk losing independence

Falls
Increased Morbidity & Mortality[2]

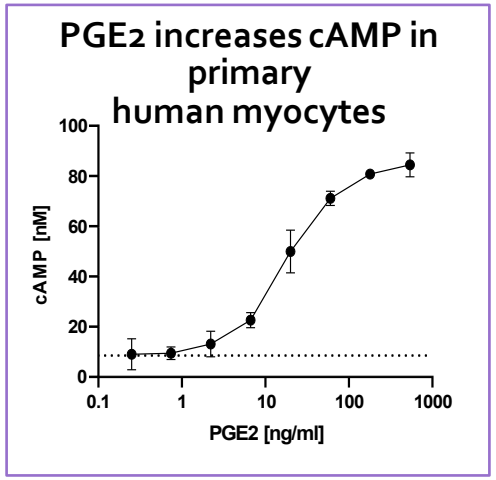
Mortality
Increased risk of death[2]

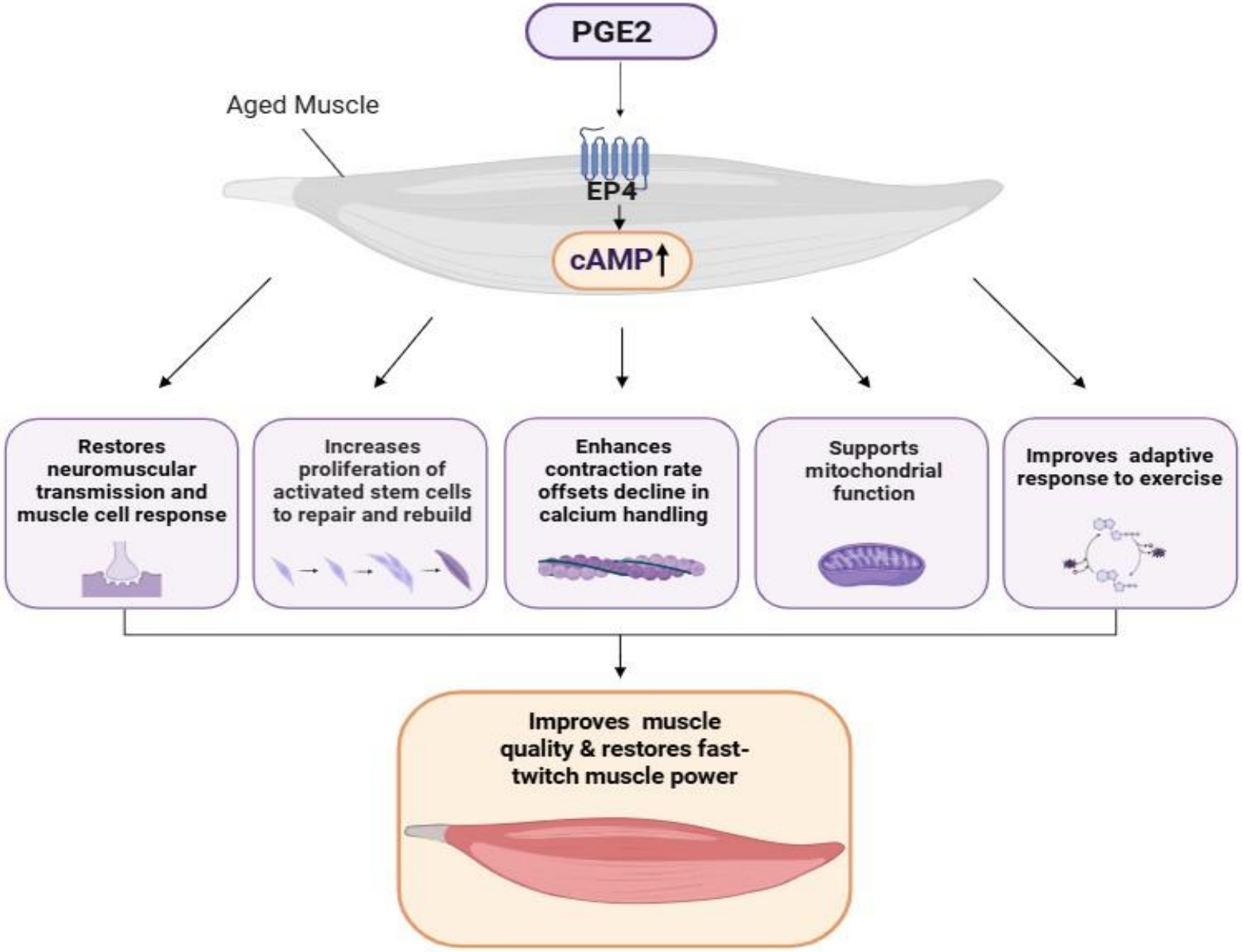


U.S. Population est. 331M

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

PGE2 Increases cAMP Resulting in Improved Muscle Quality





Berdeaux et al., 2012
Ho et al., 2017
Palla et al., 2021
Bakooshli et al., 2023
Epirium unpublished data

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

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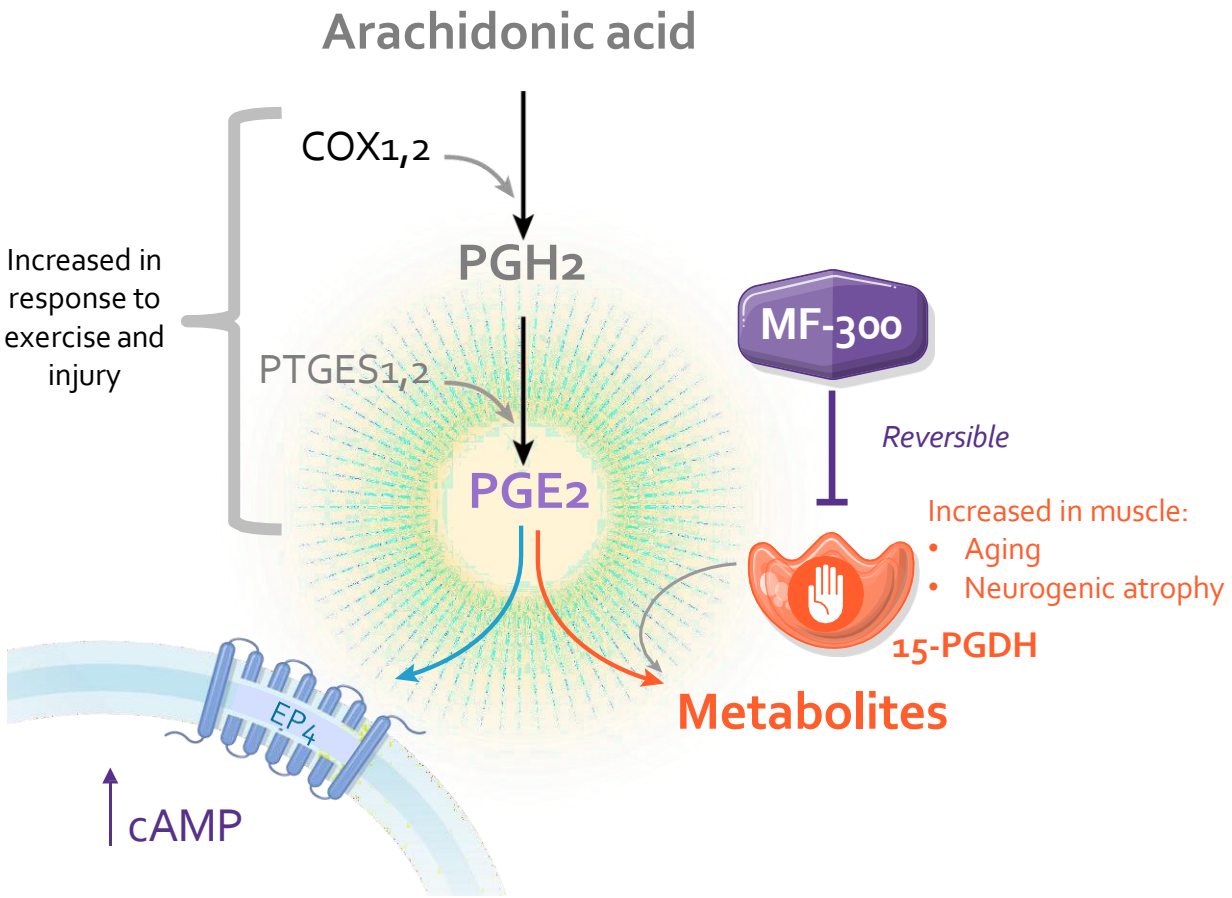
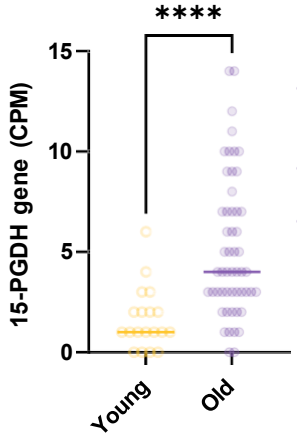
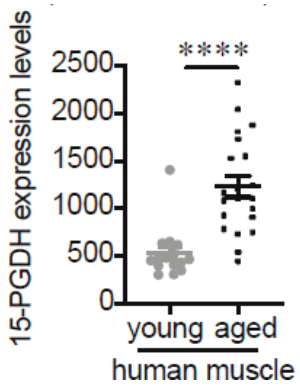
15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2



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

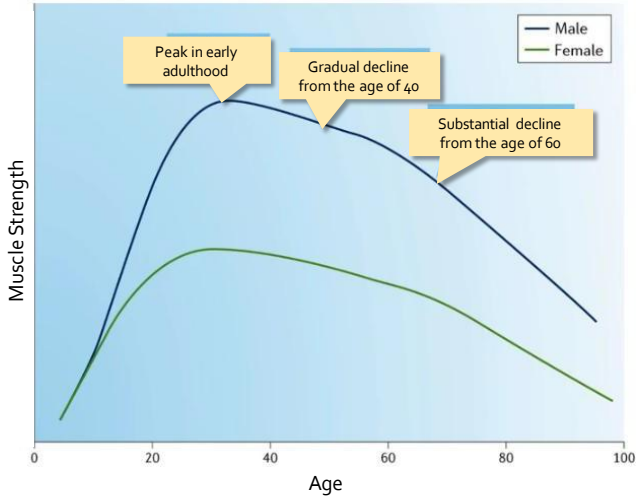


- Vastus lateralis (women and men)
- Young, N = 19 (**25±3 y.o.**)
- Older, N = 29 (**78±6 y.o.**)



- 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]



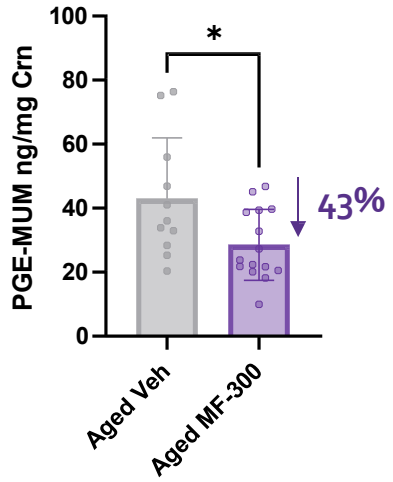
[3] GEO167186, [4] Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), [5] Dennison et al., *Nat Rev Rheum* 2017

MF-300 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

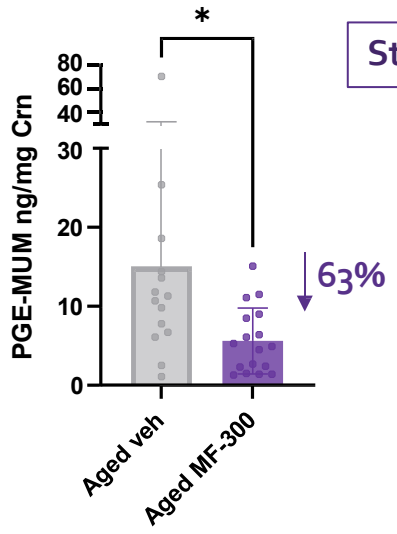


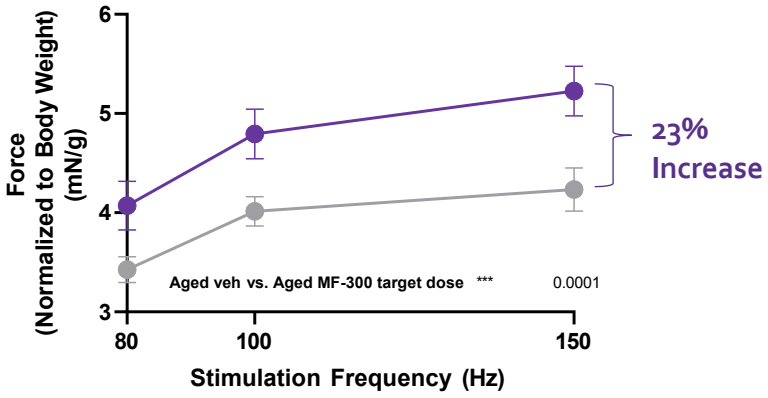
Vehicle
MF-300 target dose mg/kg

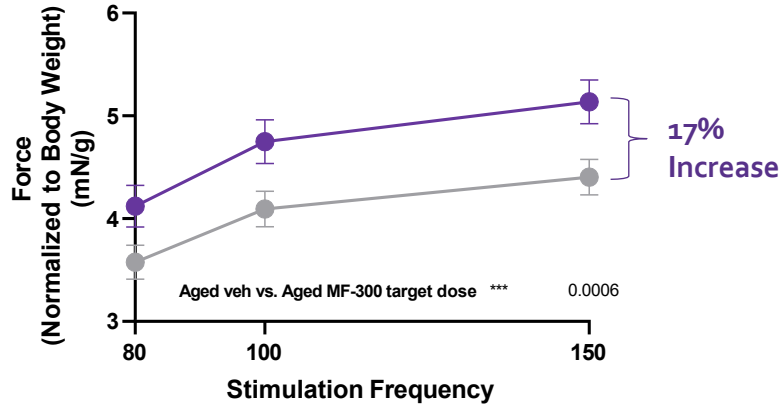
PGE-MUM
↓ ~50% average

Force
↑ ~20% average

Study 2



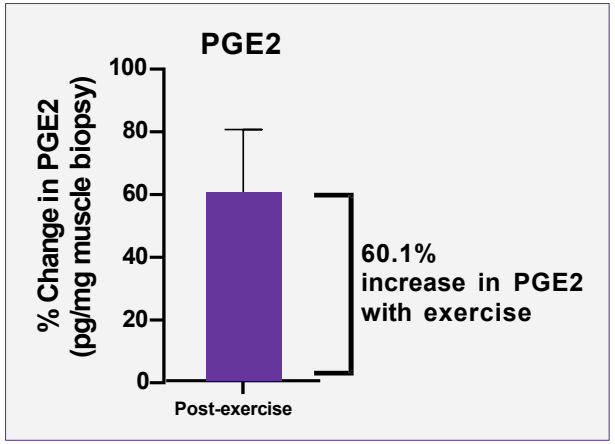




Target Engagement Biomarker

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

PGE2 in human muscle



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

Phase 1 Proof of Mechanism Study

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 older adult 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-older adult cohorts, 1 older adult 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-older adult cohorts & 1 older adult cohort

Phase 1 Clinical Success Criteria to Enable Phase 2b

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

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 2b 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)
- **Comparable safety profile between older and younger adults**

Adverse Events: No dose-limiting Toxicities

- No maximally tolerated dose identified, majority of adverse events mild, all resolved without intervention
- No dose-response in frequency or severity of AEs
- With repeat daily dosing:
  - **Younger adults:** No difference in incidence of AEs between MF-300 and placebo
  - **Older adults:** Incidence of AEs with MF-300 < placebo
- Most common AE in both populations: Mild diarrhea which was 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
- No relevant changes in eGFR
- Some fluctuations in blood pressure and heart rate consistent with placebo
- No QTc prolongation or hemodynamic concerns

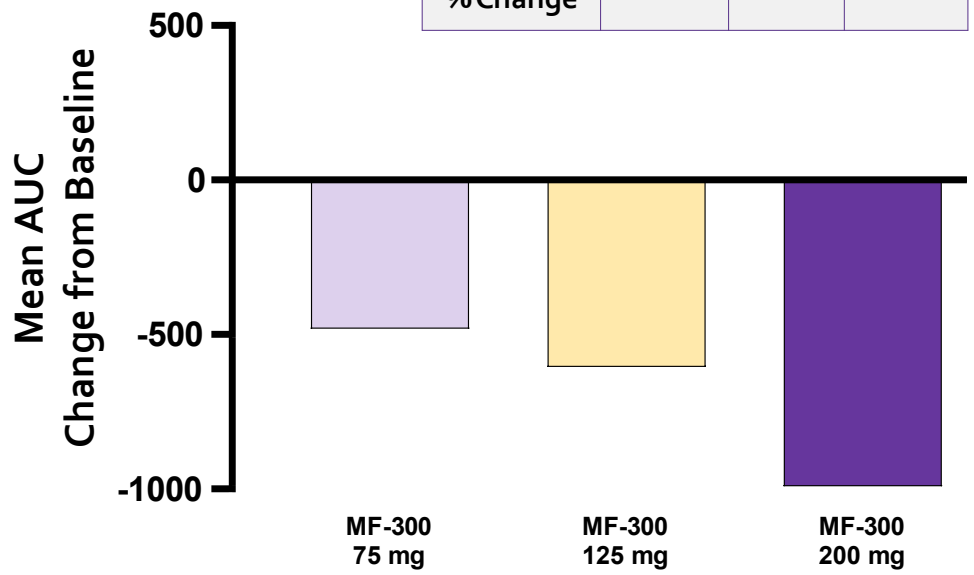
No additional monitoring required beyond standard Phase 2b assessment

Increased PGE2 Levels with MF-300 Demonstrates Proof of Mechanism

- Targeted reductions in PGE-Major Urinary Metabolite (PGE-MUM) are consistent with those associated with ~20% improvement in muscle force in sarcopenia mice model
- Increases in urinary PGE2 are consistent with those in muscle following eccentric exercise in humans

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

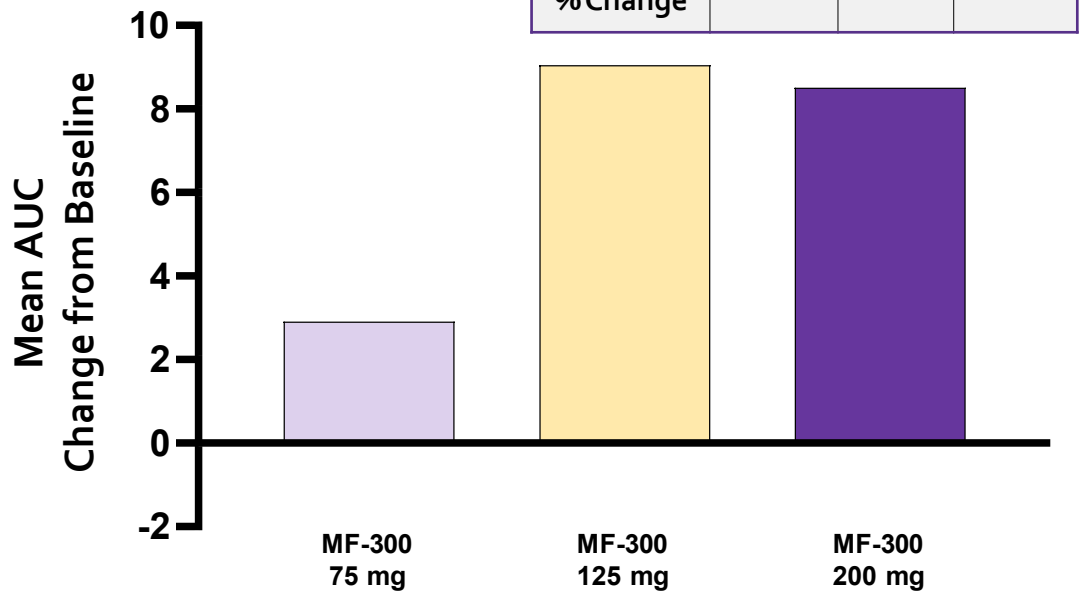
MF-300 (mg)	75	125	200
Placebo Adj. % Change	-64%	-64%	-83%*



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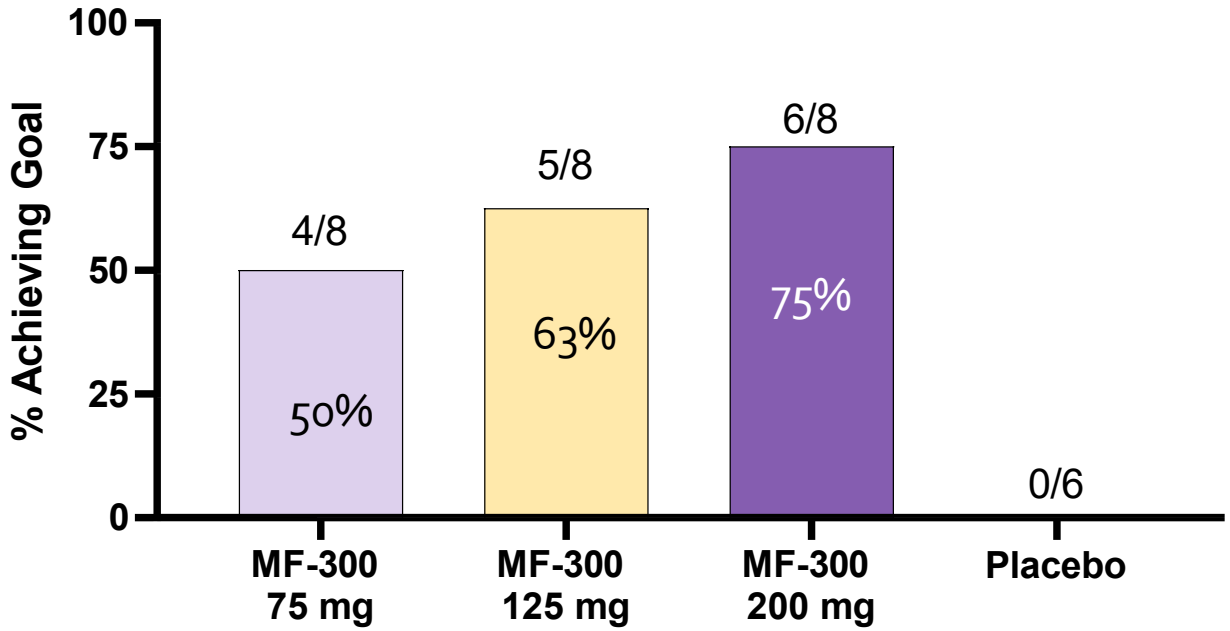
Proportion of Subjects Achieving Targeted % decrease in PGE-MUM & 60% Increase in PGE2



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

Biomarker Modulation in Older Adults Consistent with that Observed in the Younger Population

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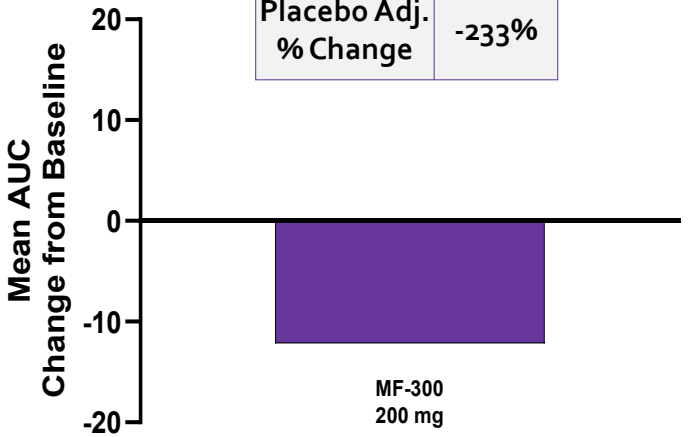
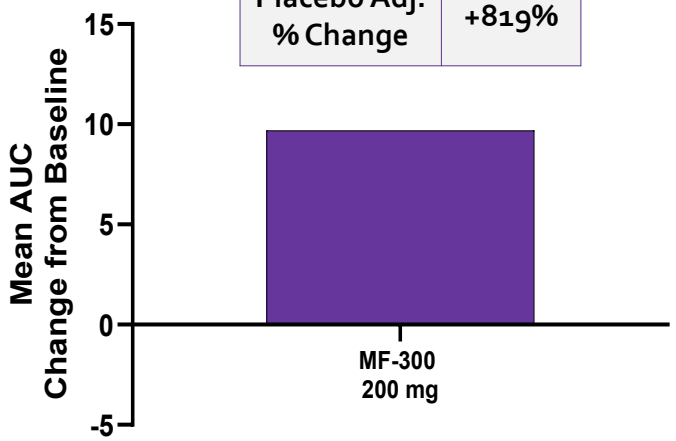
Placebo-adjusted PGE-MUM Change from Baseline

MF-300 (mg)	200
Placebo Adj. % Change	-233%

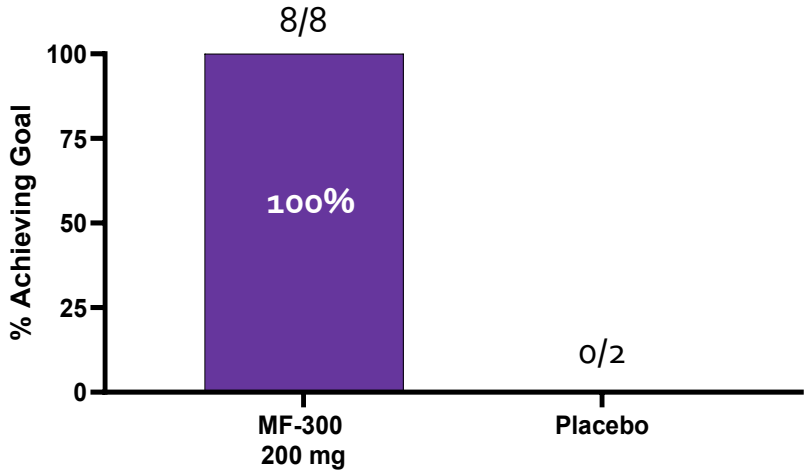


Placebo-adjusted PGE2 Change from Baseline

MF-300 (mg)	200
Placebo Adj. % Change	+819%



% Subjects with ≥50% decrease in PGE-MUM & ≥60% Increase in PGE2



MF-300 Increases the Ratio of PGE_2/PGE-MUM Consistent with Reduced PGE_2 Catabolism in Both Age Groups

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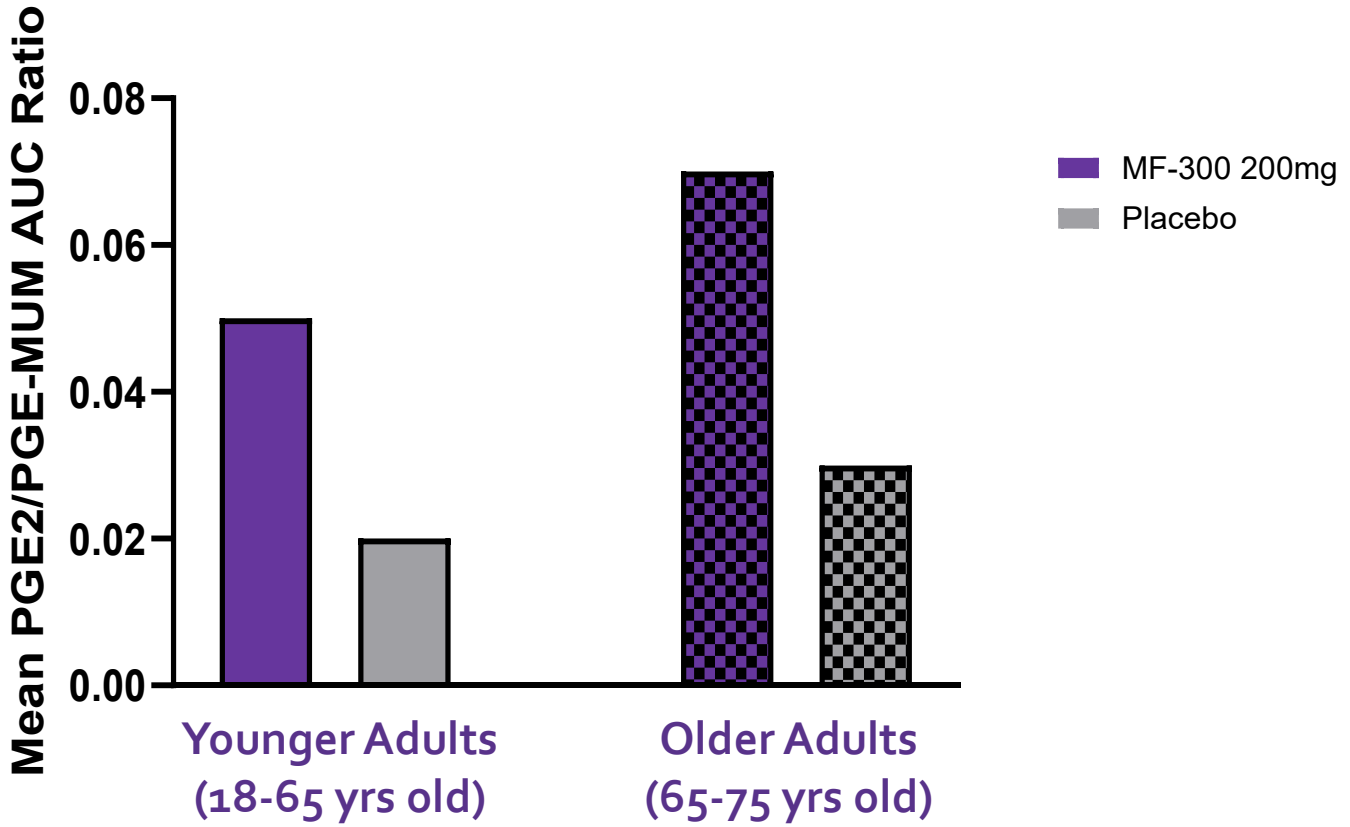
2-fold increase in PGE_2/PGE-MUM Ratio in both Age Groups– Consistent Functional Inhibition



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

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

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

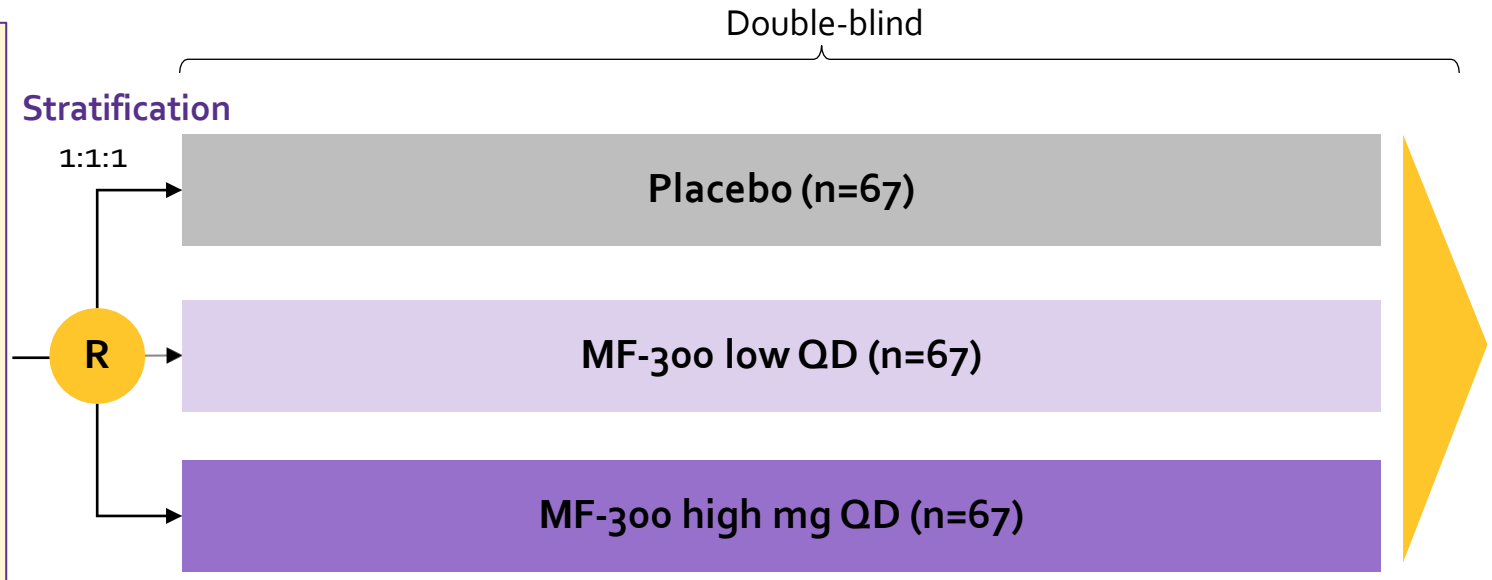
&

- 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)

Ongoing review of unblinded efficacy and safety data by DMC

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

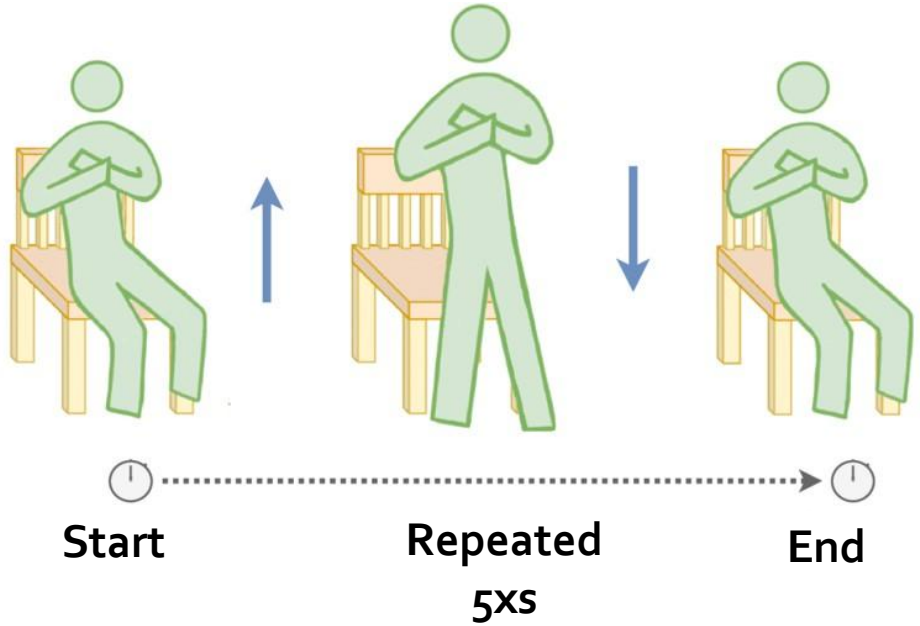
DMC=Data Monitoring Committee; EoT=end of treatment; EoS=end of study; R=randomization; SDOC=Sarcopenia Definitions and Outcomes Consortium; SPPB=Short Physical Performance Battery; Wk=week; yo=years old

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]
- **Strong predictor of clinical outcomes**
  - Activities of daily living
  - Fall Risk
  - All-Cause Mortality
- **Loss of 1 second (~10%) per year is accepted as clinically meaningful**
- **Aligns directly with MF-300's mechanism of action,** which targets fast-twitch muscle and primarily lower limb strength
- Limited variability and modifiable within 6 months

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).

Rationale for 5x Chair Stand Test (CST): Strong Predictor of Fall Risk and All-cause Mortality

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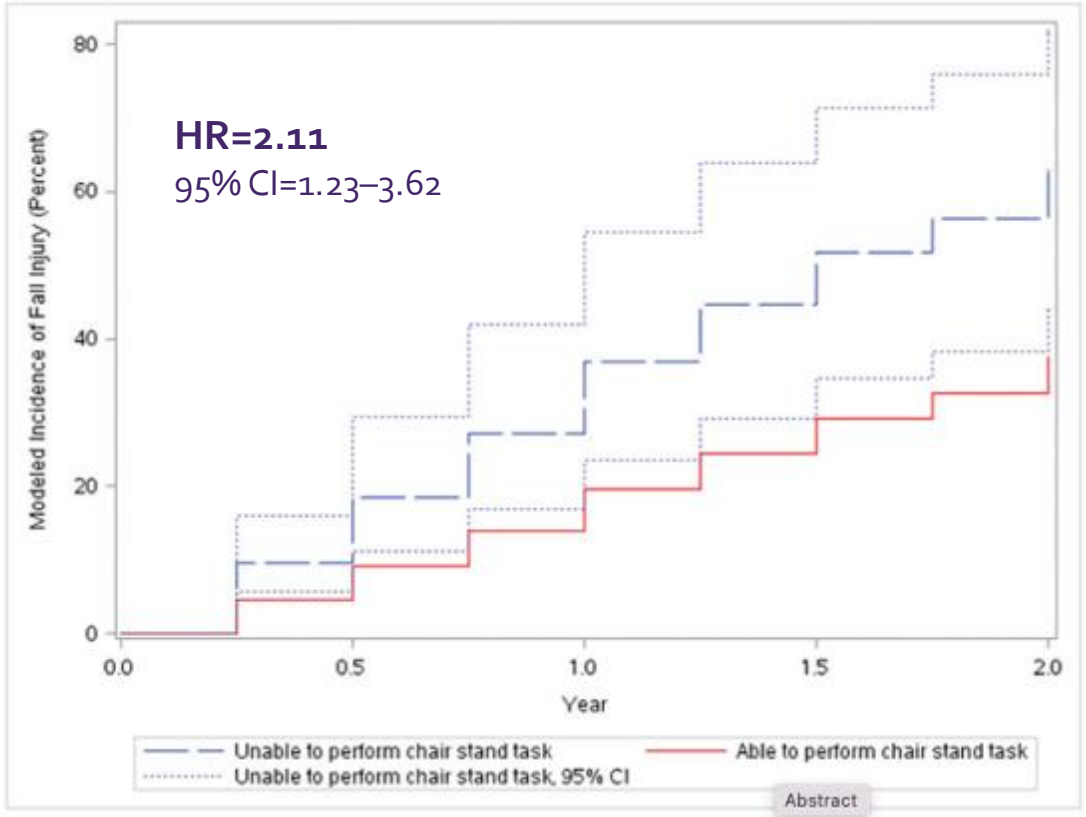
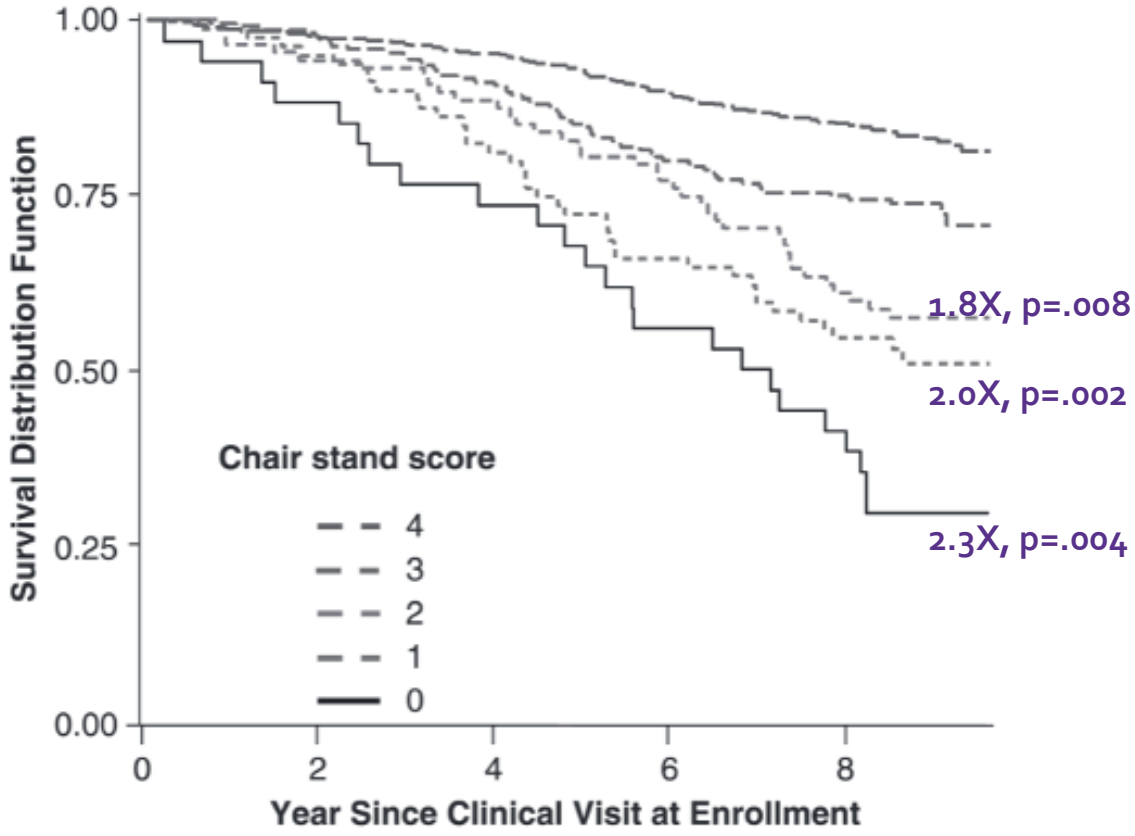
Cumulative incidence of fall-related injury by the ability to perform 5XCST[1]



Survival curves during 9 years of follow-up by time to complete the 5X CST[2]



1. Shea et al.; Am J Phys Med Rehabil. 2018; 97(6): 426–432
2. Bandinelli et al., J Am Geriatr Soc. 2009; 57(11): 2172–2173

Positive Type C (End-of-Phase 1) FDA Meeting Supports Advancement of MF-300 to a Phase 2b Study in Sarcopenia

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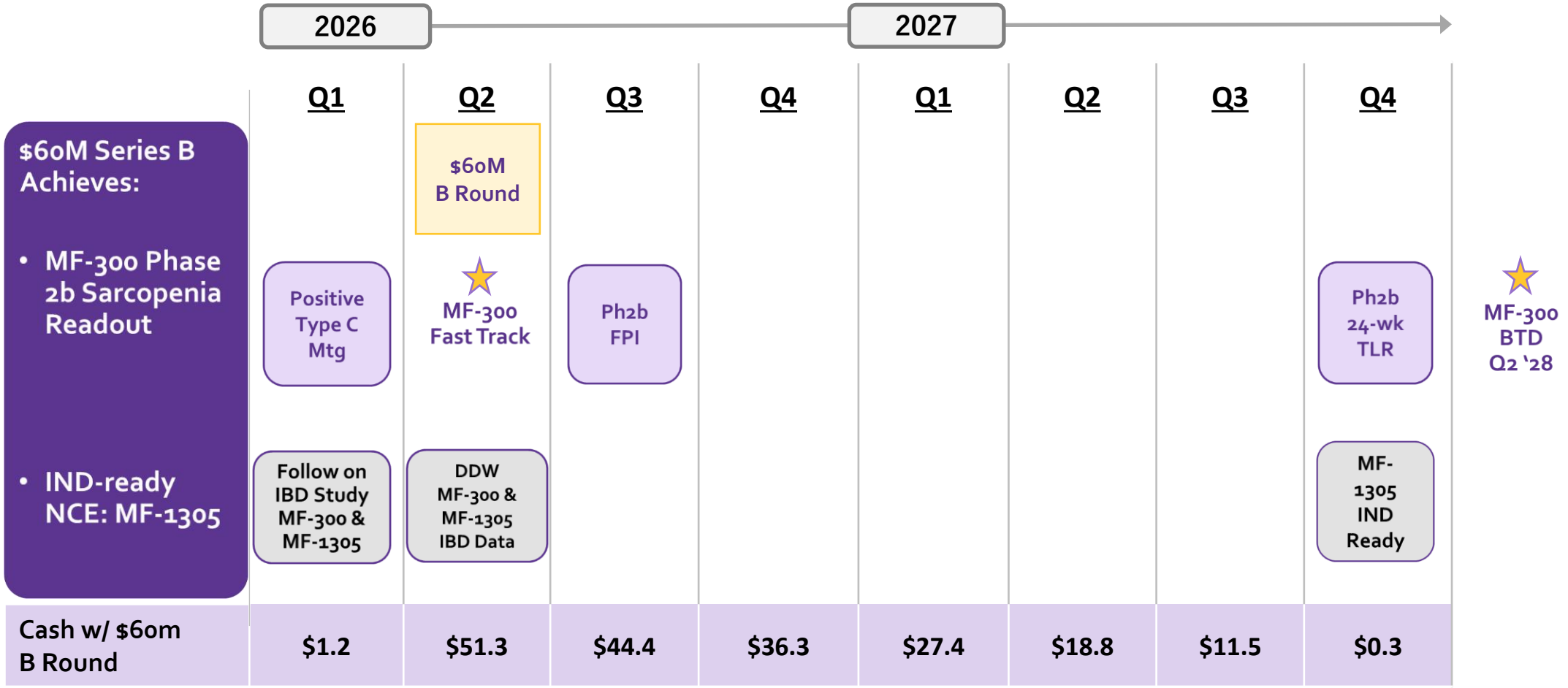
Key Outcomes

- The FDA's written feedback was overall positive and constructive
- Reached concurrence with FDA on the patient population, primary and secondary efficacy endpoints, treatment duration and dosing regimen of MF-300
- Agreement that the efficacy endpoints evaluated in the Phase 2b study will inform Phase 3 endpoint selection
- Agreement that a Fast Track Designation request may be submitted for MF-300 as a treatment for sarcopenia.

"In the absence of approved pharmacologic therapies or established regulatory pathways for sarcopenia, alignment with the FDA on a Phase 2b trial design represents an important milestone for the field," said Dr. Jose Garcia, M.D., Ph.D., Professor, Department of Medicine, Division of Gerontology and Geriatric Medicine, University of Washington School of Medicine.

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

Epirium Bio



Additional $30M ($90M raise) enables Phase 3 CMC commencement bringing forward MF-300 Commercial Launch 6 months to 1H 2032

Back-up Section

- MF-300 force improvement comparison to apitegromab in Translational Delta7 SMA Mouse Model
- Epirium's Sarcopenia Development Council

MF-300 Attractive Profile in Translational SMA Model in Mice

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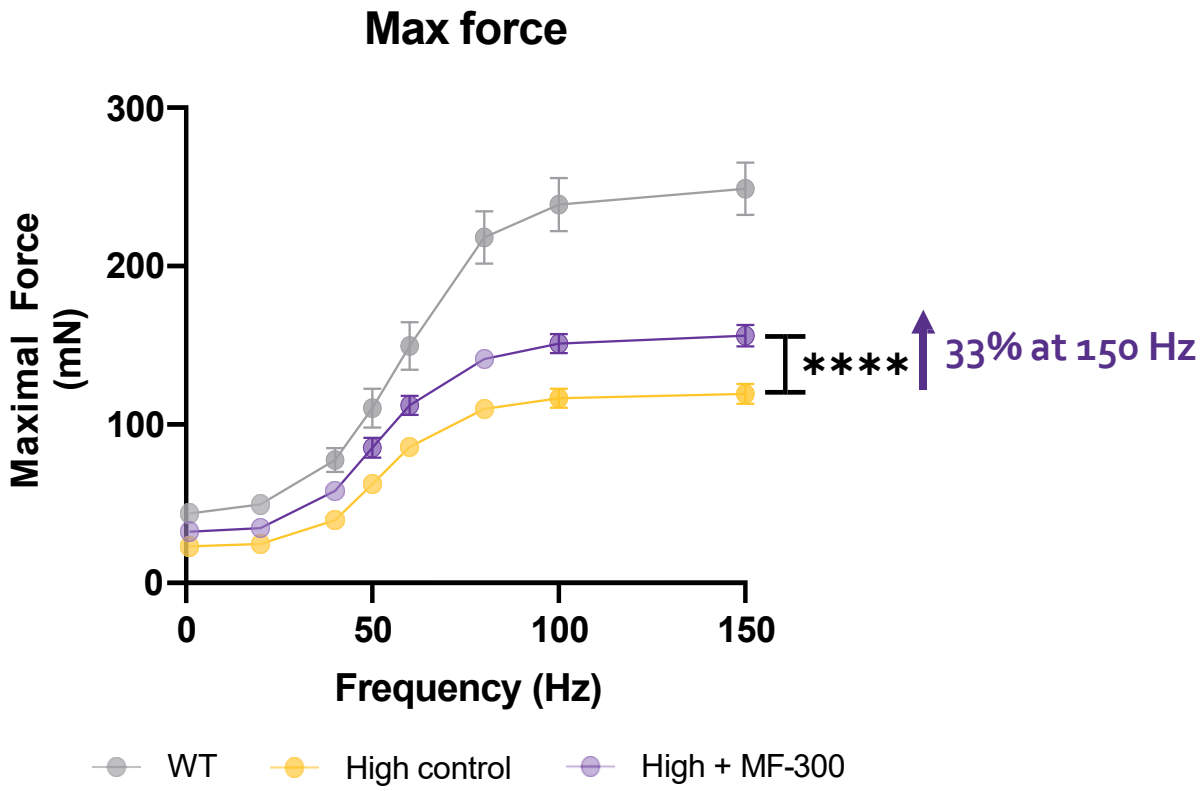
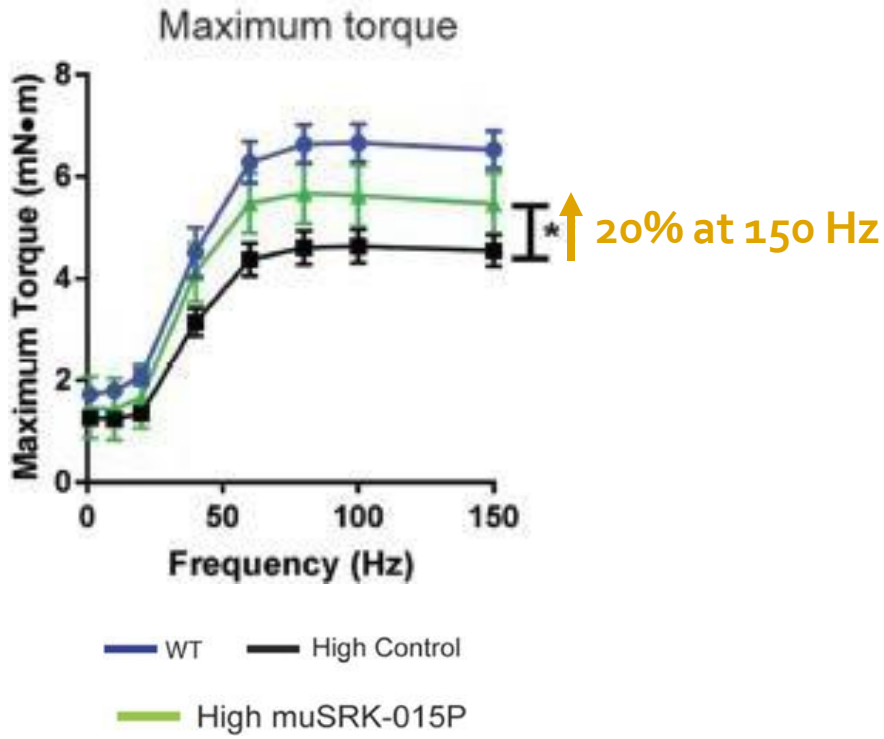
MF-300 in SMNΔ7 High/High Male mice



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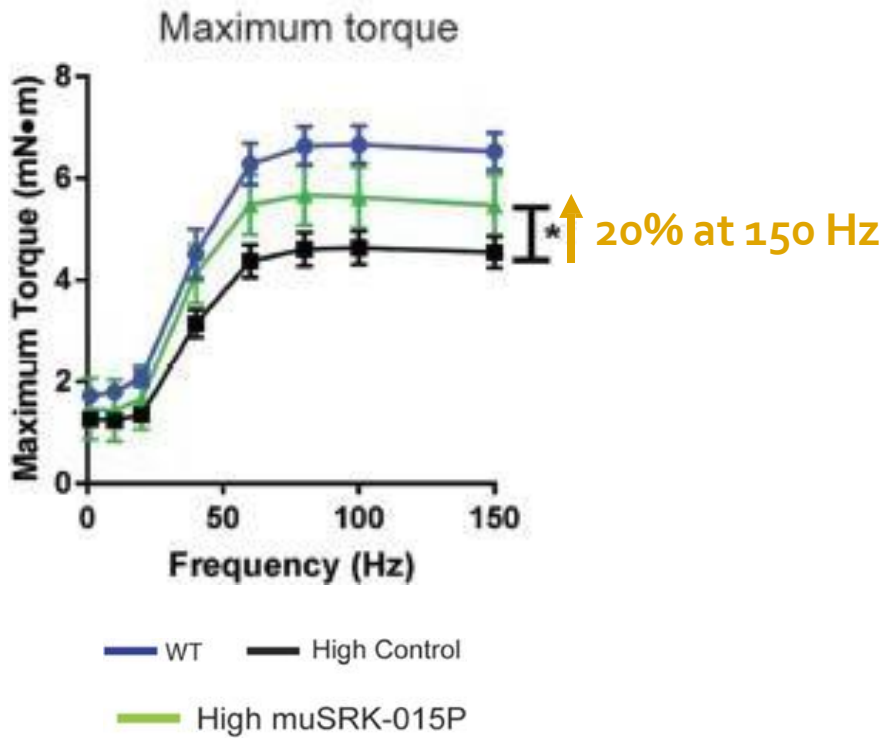
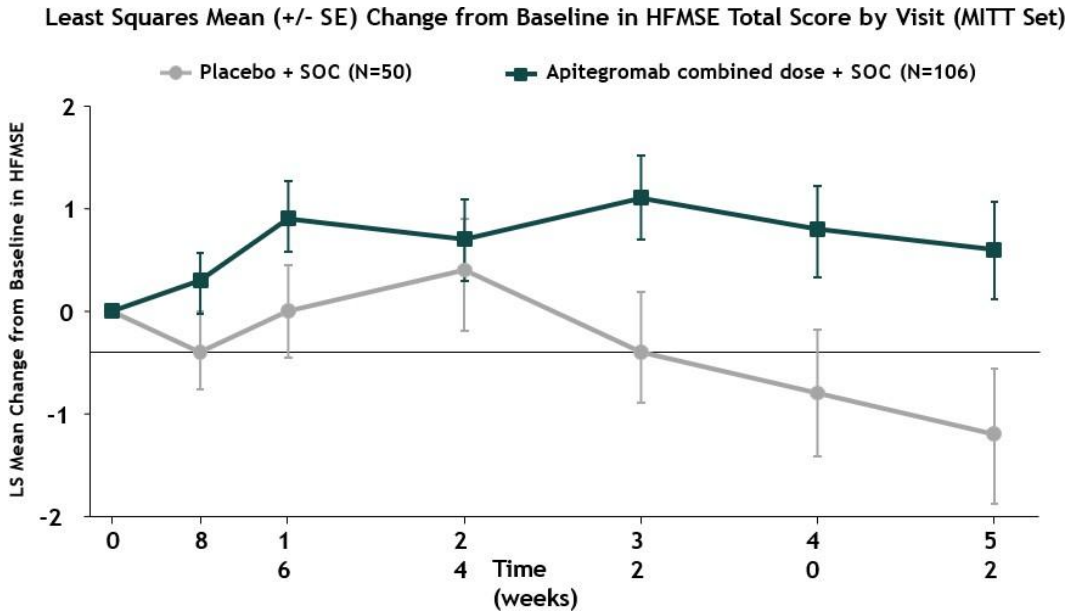
Demonstrates that a 20% increase in isometric plantar flexor force in mice translates to clinical benefit

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

Epirium Sarcopenia Clinical Development Advisors

David Cella, PhD

Director, Institute for Public Health and Medicine (IPHAM)

Northwestern University
International leader in PRO

Key leader in the development of PROMIS®

FDA advisor on Care Outcome Set

Scott Delp, PhD

Founding Chairman of the Department of Bioengineering at Stanford

Stanford, Wu Tsai Center Biomedical Engineering

Stanford engineer pioneering biomechanics, muscle performance, and wearable monitoring technologies.

Jerome Feige, PhD

Adult Health Science Lead & Senior Expert in Musculoskeletal Health

Led drug discovery for muscle diseases at Novartis, contributing to development of new therapies

Built muscle biology and translational programs leading to commercialization of several products and start-ups.

Roger Fielding, PhD

Co-Director, Boston NIA Center

Tufts University

Researcher studying the underlying mechanisms contributing to the age-associated decline in skeletal muscle mass. Published landmark studies in sarcopenia, frailty and muscle function. Conducted numerous studies examining the roll of skeletal muscle power on physical performance in older adults.

Jose M. Garcia, MD, PhD

Physician-Scientist at the Puget Sound VA Health Care System

University of Washington, Seattle

Directing the Clinical Research Unit and the GRECC. Expert in wasting disorders, leading basic and clinical research on ghrelin, androgens, and other anabolic pathways.

Jack Guralnik, MD, PhD

Professor, Epidemiology & Public Health

U of Maryland, Medical School

Developed the SPPB, a gold-standard functional outcome; expert in disability and mobility trials.

George Kuchel, MD

Professor of Medicine, Travelers Chair in Geriatrics and Gerontology, and Director of the UConn Center on Aging and Pepper Center

University of Connecticut

Researcher studying functional decline, mobility, and cognition, in older adults, with a mission of precision gerontology to tailor interventions to individual variability.

Nathan K. LeBrasseur, PhD

Director, Robert & Arlene Kogod Center on Aging

Mayo Clinic

Noaber Foundation Professor of Aging Research

Department of Physical Medicine & Rehabilitation

Department of Physiology & Biomedical Engineering

Naomi Lowy, MD

Principal Drug Regulatory Expert

Hyman Phelps

Fmr. FDA, Deputy Dir. Endocrinology Division

At FDA, provided leadership in drug policy and drug development in sarcopenia.