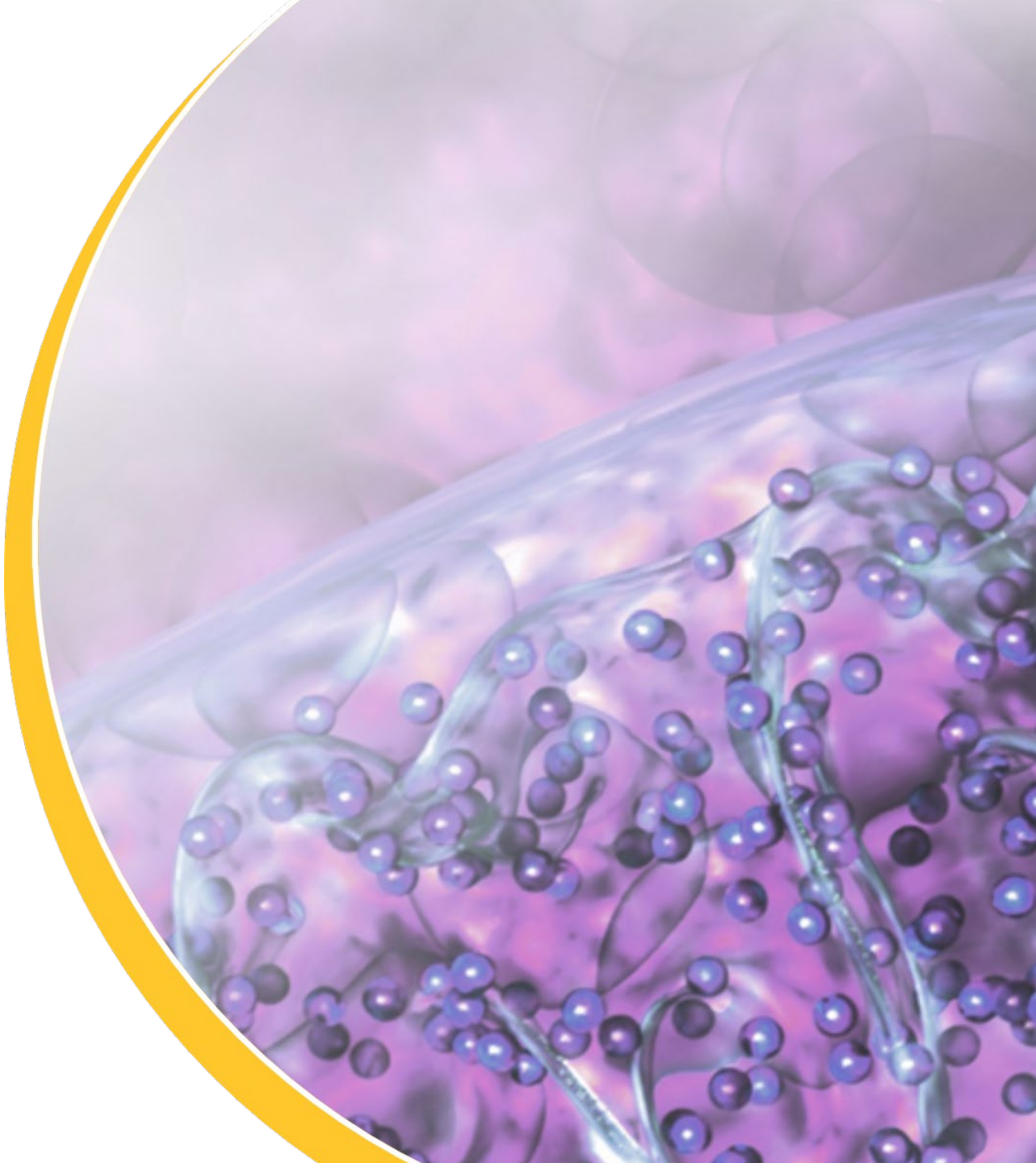
Epirium Bio

Oral 15-PGDH Inhibitor Platform:

Leveraging PGE2 Signaling to Treat Sarcopenia, Neuromuscular & Inflammatory Diseases (IBD):

- MF-300 in Phase 2b Start-up for Sarcopenia



Experienced Team with a Demonstrated Track Record of Success

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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)

Leigh MacConell, Ph.D. Chief Development Officer

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

Eric Miller, CFO

Head Finance, Synthorx (acquired by Sanofi)

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

Cadence Pharm. (acquired by Mallinckrodt)

Consultant Advisors

Daniel Cooper, M.D. Medical Lead

Over 20 years in drug development

Formerly VP Pharmacovigilance Orexigen, Affymax; Clinical and Safety Scientist roles at Roche, Johnson & Johnson

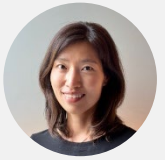
Multiple successful NDAs supporting pre- and post-marketing approvals

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

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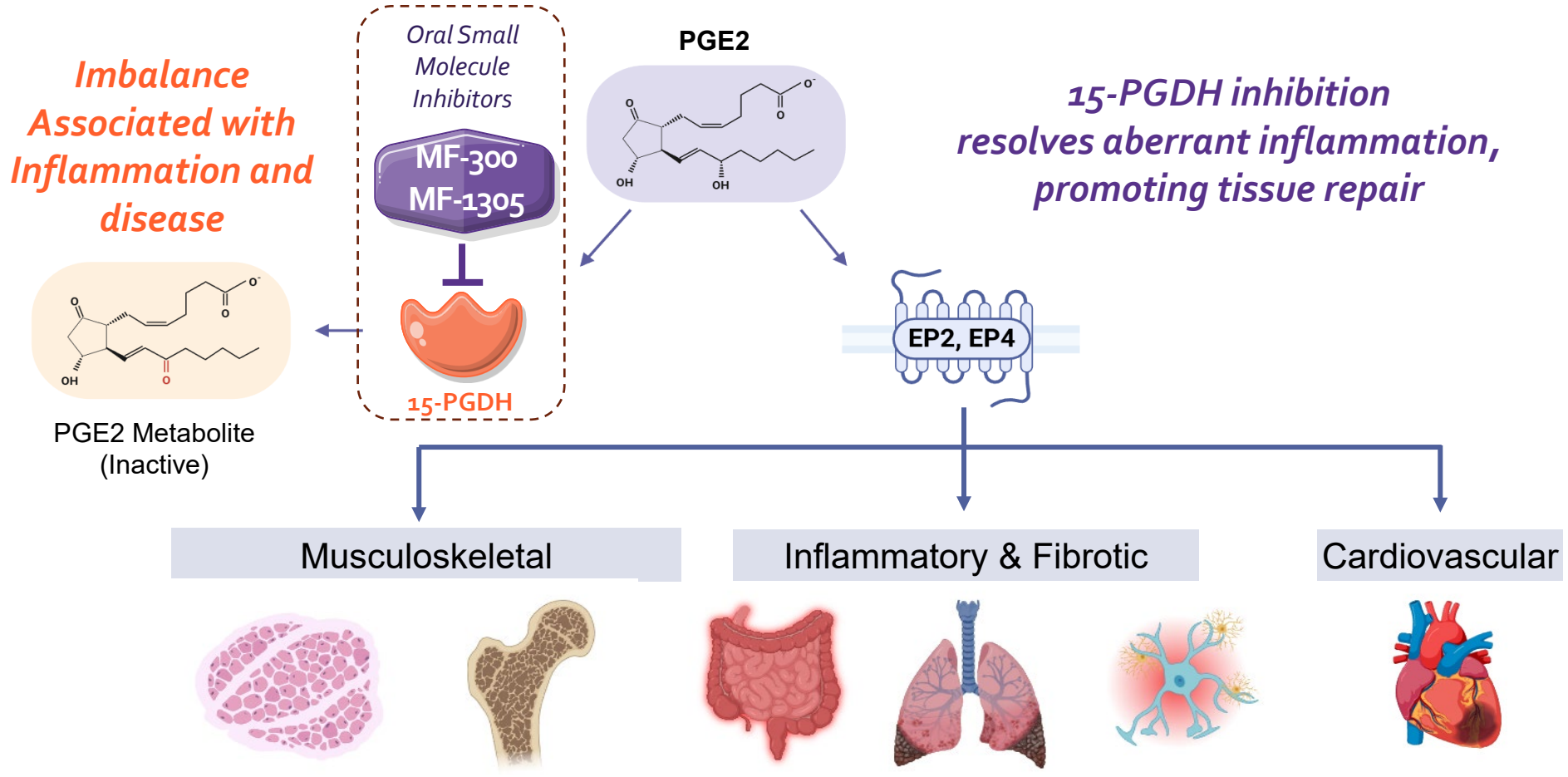
Inhibiting 15-PGDH to leverage the potential of PGE_2 to promote tissue function



✓ = POC Achieved

- ✓ **Sarcopenia** Sarcopenic Obesity
- ✓ **Rare Neuromuscular (SMA)**
- ✓ **Osteoporosis** OA/cartilage
- ✓ **Ulcerative Colitis** Crohn's Disease
- ✓ **IPF**
- Neuro-Inflammation
- Heart Failure

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

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	Therapeutic Area	15-PGDH INHIBITOR (Oral)	PRECLINICAL / IND ENABLING / PHASE 1 / PHASE 2
Musculoskeletal	**Sarcopenia** *Potential label expansion: Sarcopenic obesity*	MF-300	Phase 2b in start-up
Musculoskeletal	**Osteoporosis***	MF-300	Phase 2 ready
Musculoskeletal	**Spinal Muscular Atrophy (SMA)**	NCE	Preclinical Efficacy
Inflammatory / Fibrotic	**Irritable Bowel Disease (IBD)**	NCE	Preclinical Efficacy
Inflammatory / Fibrotic	**Idiopathic Pulmonary Fibrosis**	NCE	Preclinical Efficacy

MF-300 Upcoming Milestones:

- Ph2 Open-label:
  - FPI: Q4 '27
  - 12-week Data: Q2 '27
  - 24-week Data: Q3 '27
- Ph2 Double Blind:
  - FPI: Q1 '28
  - Top Line Data: Q1 '28

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

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Epirium Lead Program in Sarcopenia:

- Unmet Need
- Scientific Rationale
- Preclinical Muscle Force
- Bone Microarchitecture data
- Published Cartilage Data

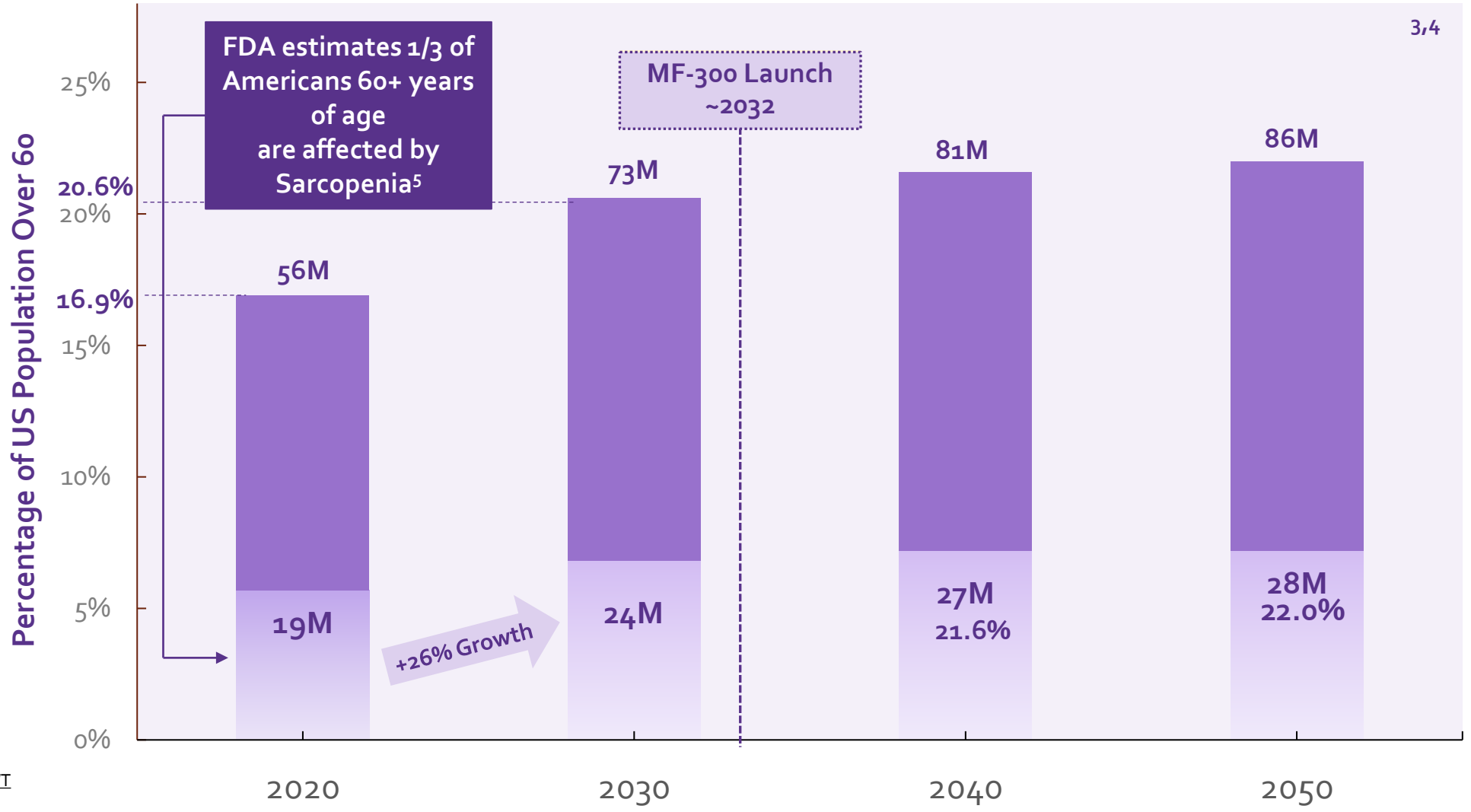
Sarcopenia: Large and Growing Unmet Medical Need w/ No FDA Approved Therapy

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

Dependence
Increased risk losing independence

Falls
Increased fracture risk & hospitalization, >2-fold greater cost[2]

Mortality
2-fold 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–EP4 Signaling Elevates cAMP to Promote Muscle Function

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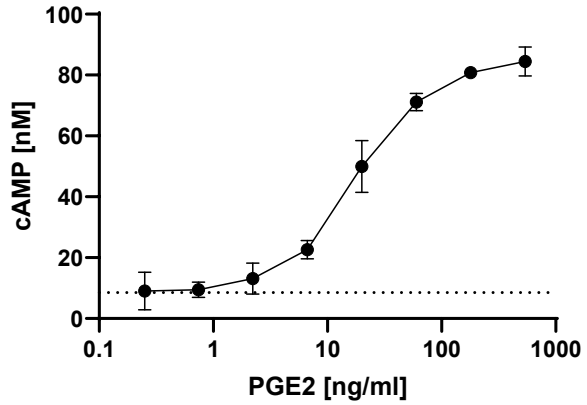
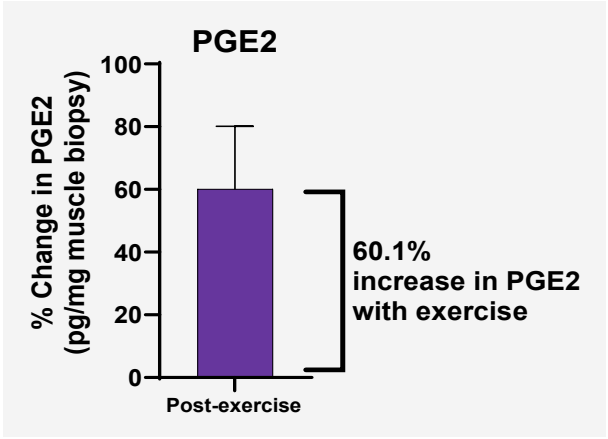
PGE2 increases cAMP in primary human myocytes

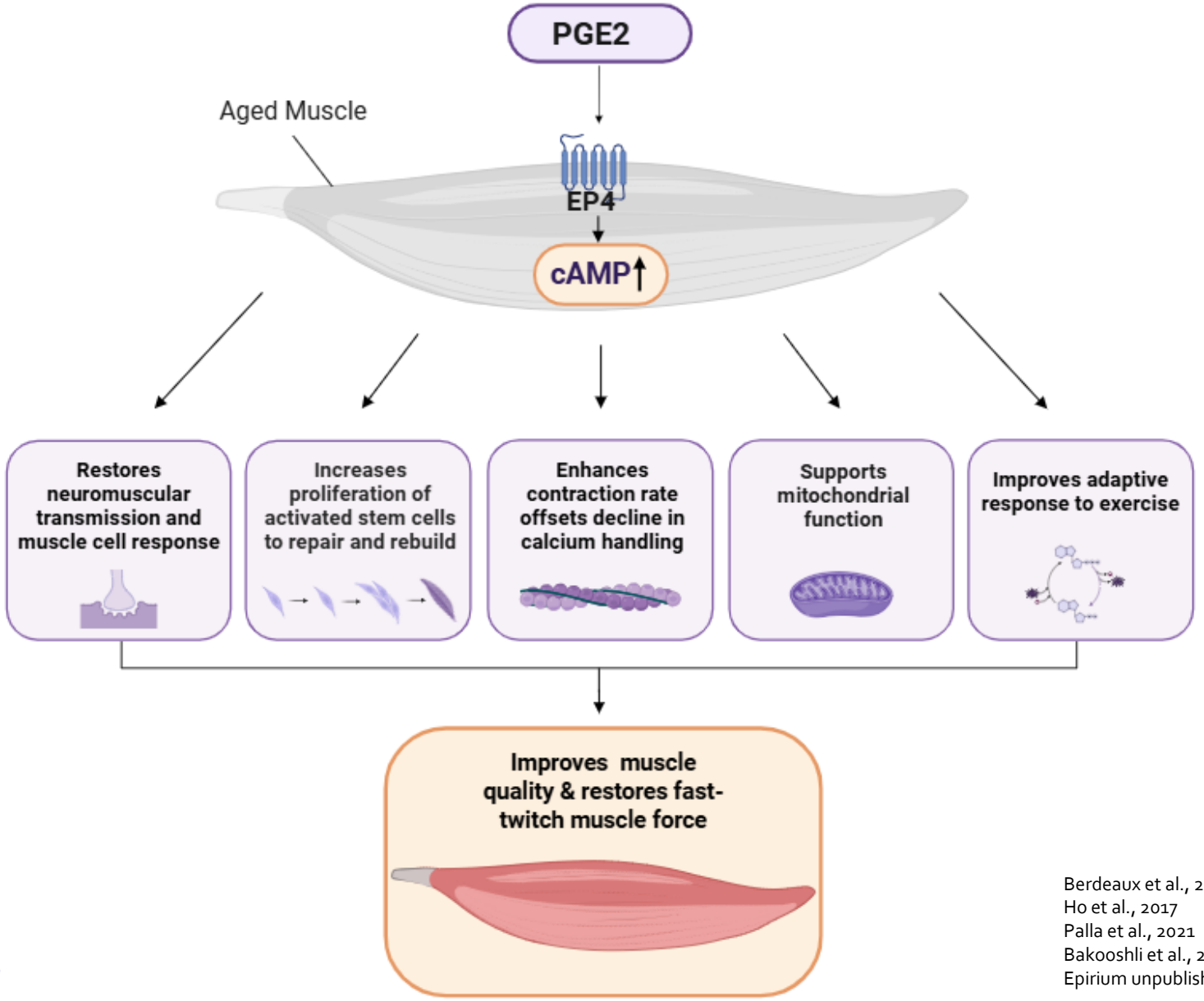


Epirium unpublished data

PGE2 in human muscle following exercise



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



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

15-PGDH, an Enzyme that Degrades PGE2, is Upregulated in Aged Muscle

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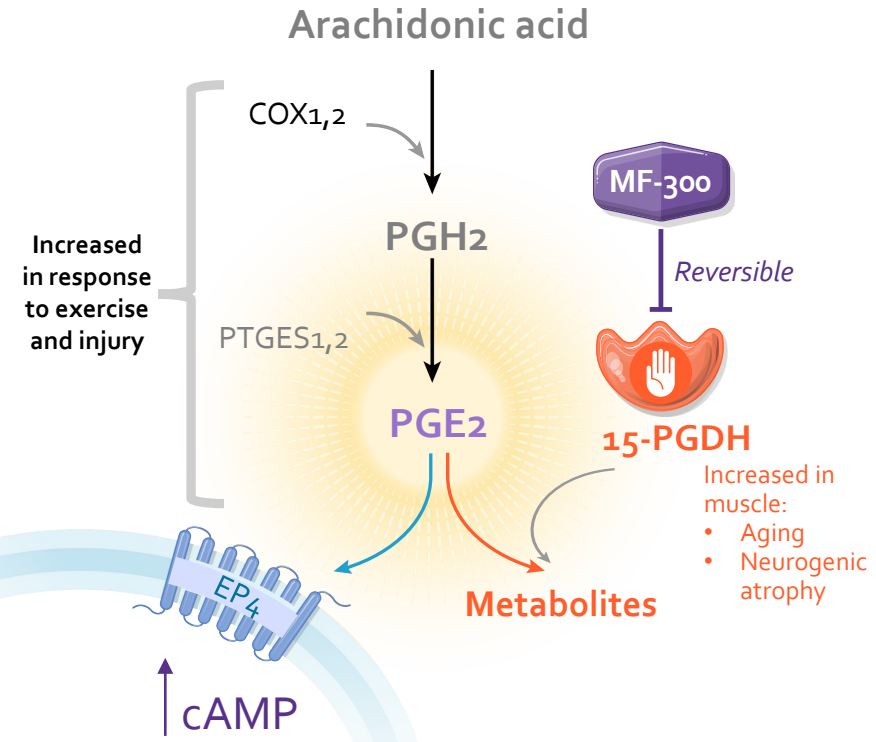
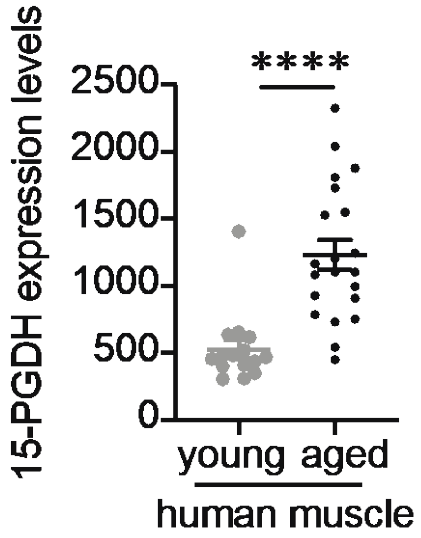
15-Hydroxyprostaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2

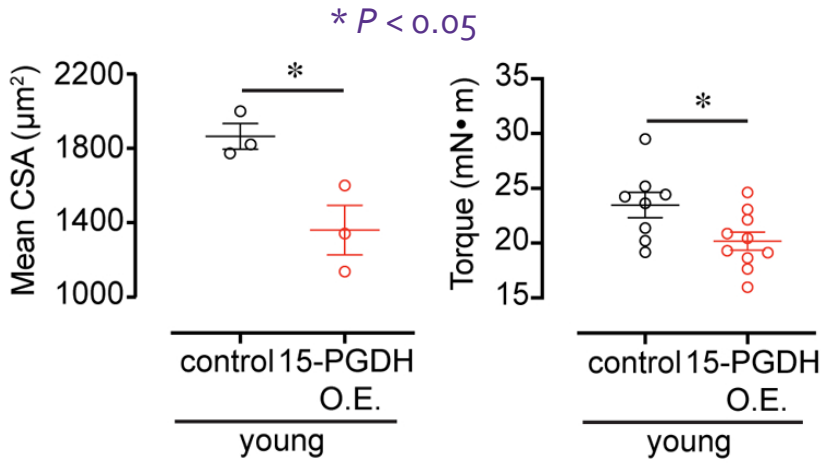


15-PGDH expression Elevated in aged human muscle[1]



- Vastus lateralis (microarray)
- Younger, N=15 (**25±3 y.o.**)
- Older, N=21 (**78±6 y.o.**)
- **** $P < 0.0001$

15-PGDH overexpression (O.E.) Reduces myofiber cross-sectional area (CSA) and muscle force[2]



cAMP, cyclic adenosine monophosphate; COX1,2, cyclooxygenase enzymes 1 and 2; PGE2, prostaglandin E2; PGH2, prostaglandin H2; PTGES1, 2, prostaglandin E synthase 1,2; y.o., years old

[1] Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), [2] Palla et al., *Science 2021*

MF-300 Engages Its Target *In Vivo* — Validating the 15-PGDH Mechanism

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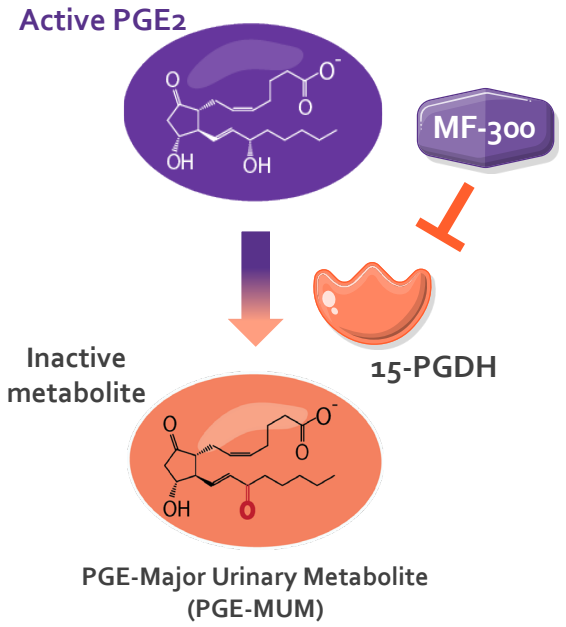
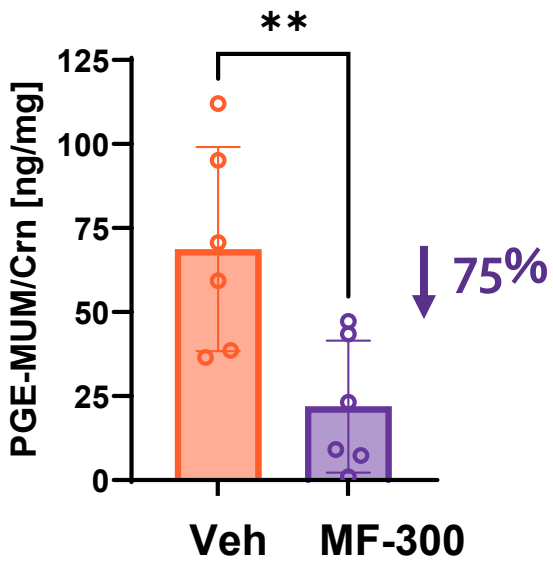
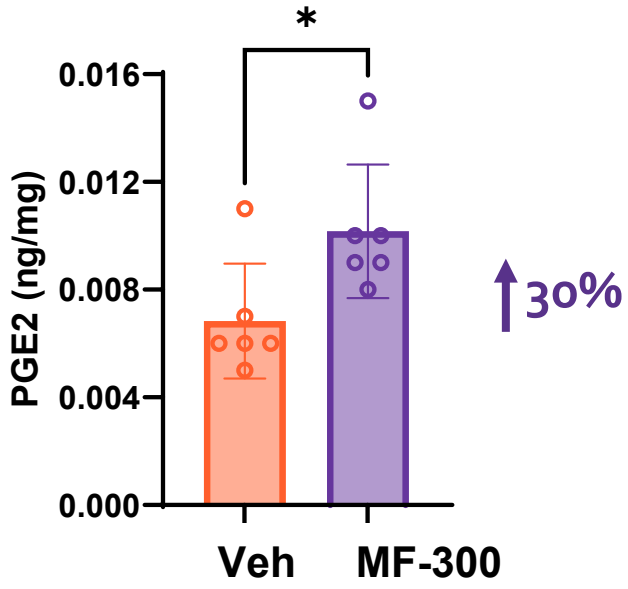
Target engagement should increase PGE2 and reduce metabolites



MF-300 decreases urinary PGE2 metabolite (PGE-MUM)



MF-300 increases muscle PGE2 (gastrocnemius)



*P<0.05, **P=0.002

PGE2 substrate up, its metabolite down — the signature of 15-PGDH inhibition

Improving Muscle Quality (Intrinsic Strength) Addresses High Unmet Need in Sarcopenia

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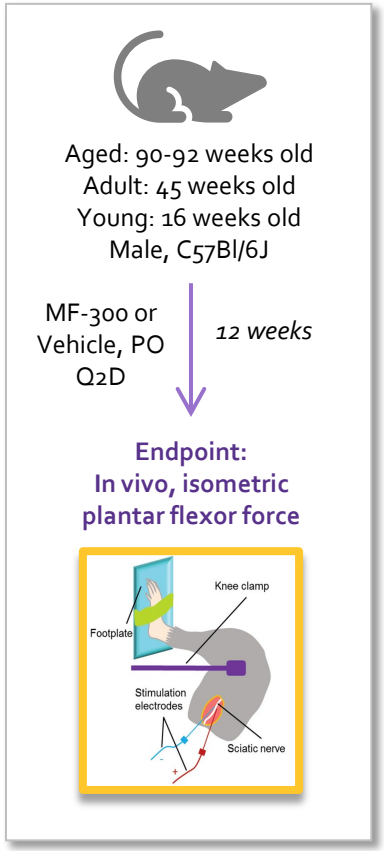
Sarcopenia Core Deficits		MF-300 therapeutic effects	
Age-related ↓ muscle force	→	↑ absolute and specific force in aged muscle	✓
Fast-twitch muscle disproportionately lost → ↓ muscle power	→	↑ fast twitch muscle contractility	✓
Reduced translational capacity → less protein synthesis	→	↑ ribosomal abundance, restoring translational capacity	✓
Neuromuscular junction degradation	→	↑ pre- and post-synaptic proteins → supports neuromuscular transmission	✓
Age-related ↑ in cortical porosity and bone perimeter → frailty and falls	→	Shifts cortical bone structure back toward young; porosity trending lower	✓

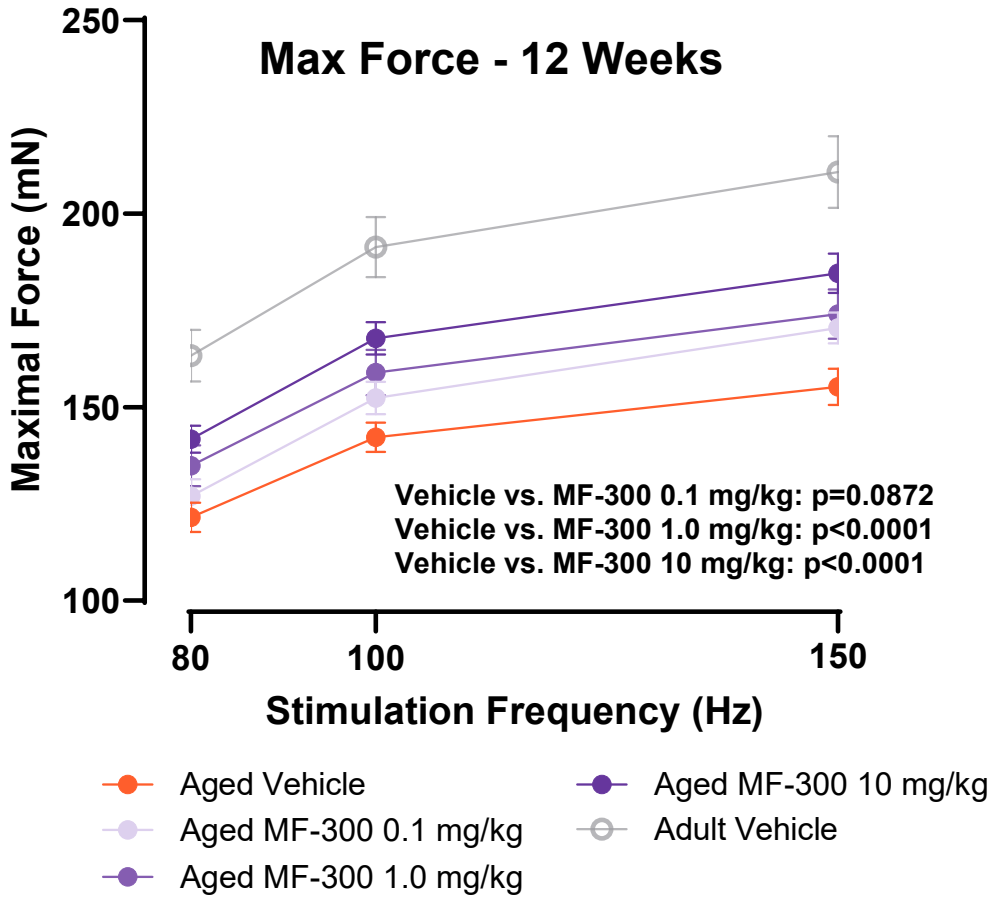
↑ urinary PGE2 levels and ↓ PGE-MUM demonstrates target engagement and use as translational biomarkers

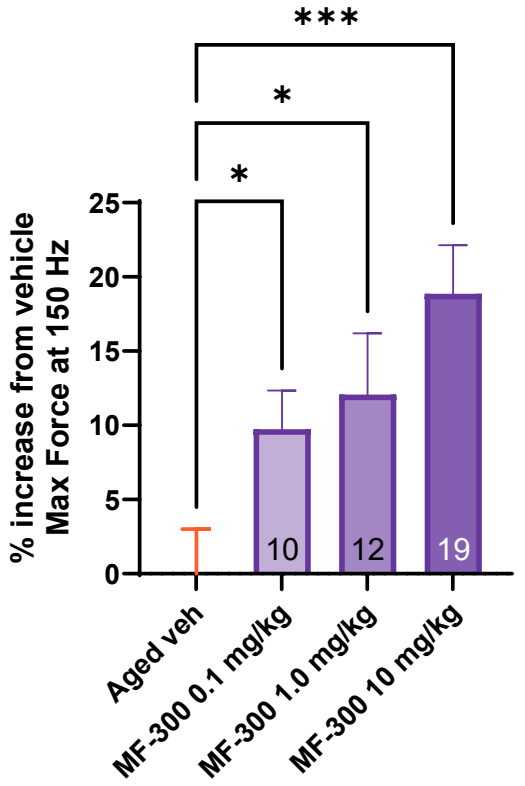
PGE2, prostaglandin E2; PGE-MUM, prostaglandin E major urinary metabolite

MF-300 Restores Muscle Force in Aged Mice

- Dose-dependent improvements in force, with up to +19% gain; **MF-300 10 mg/kg restored >50% of the strength lost to aging in only 12 weeks**
- Largest gains observed at higher stimulation frequencies — consistent with recovery of fast-twitch fibers



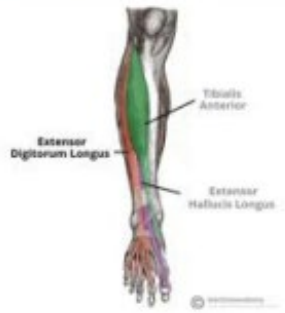




MF-300 Increases Force and Contraction Rate in Aged Fast-Twitch Muscle (*Ex Vivo*)

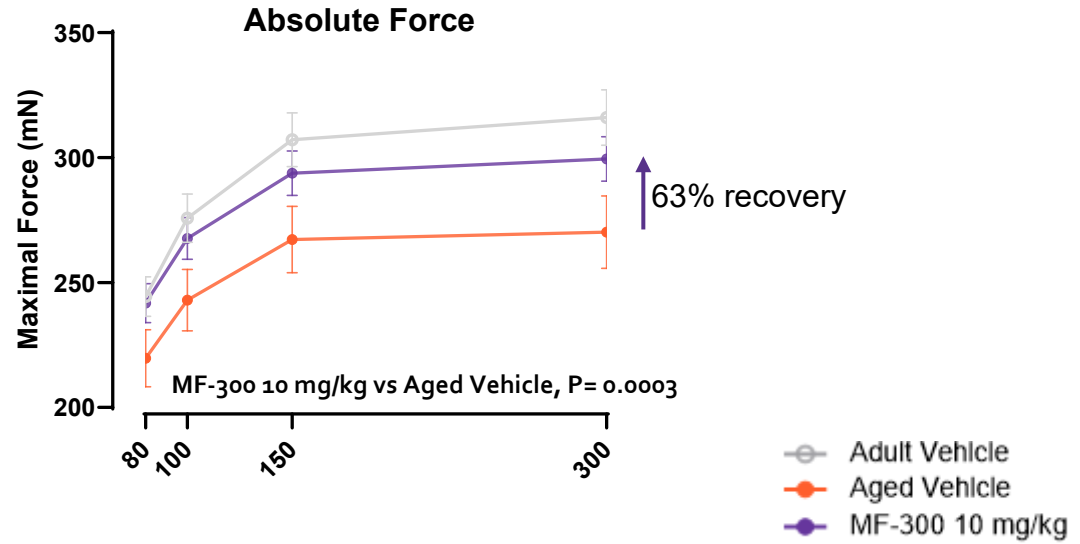
- **Maximal force increased ~10%** in aged EDL vs. aged vehicle – Recovering 63% of the strength lost to aging
- **Maximum contraction rate increased ~20%** (66% recovery) — consistent with restored type II / fast twitch fiber function
  - *Ex vivo* prep isolates the effect to intrinsic contractile function

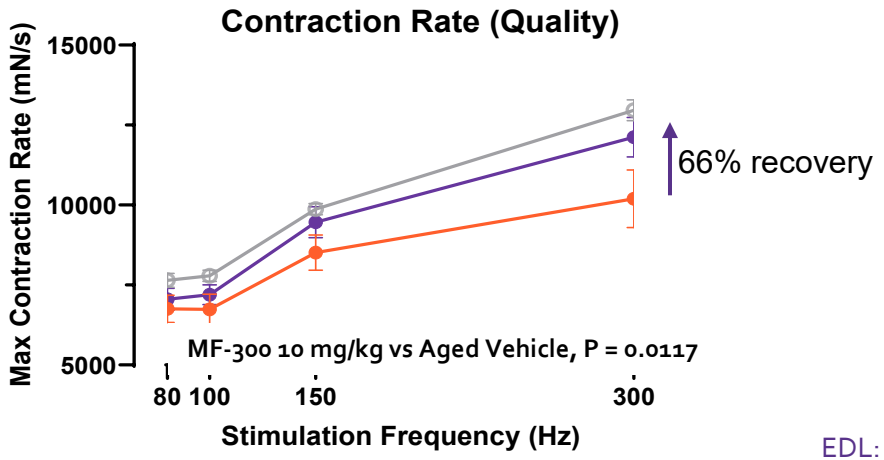
Mouse EDL is predominantly fast twitch



Ex vivo isometric force measurement

Image courtesy of Myologica



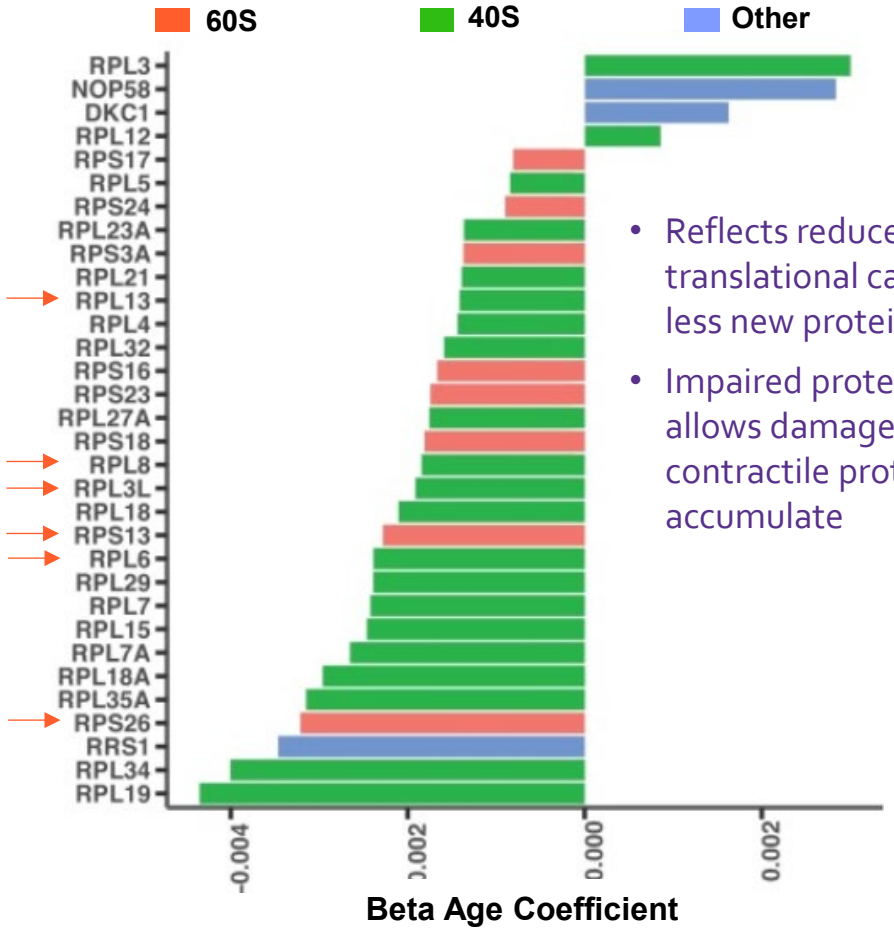


EDL: extensor digitorum longus

MF-300 Restores Ribosomal Proteins Lost in Human Aging

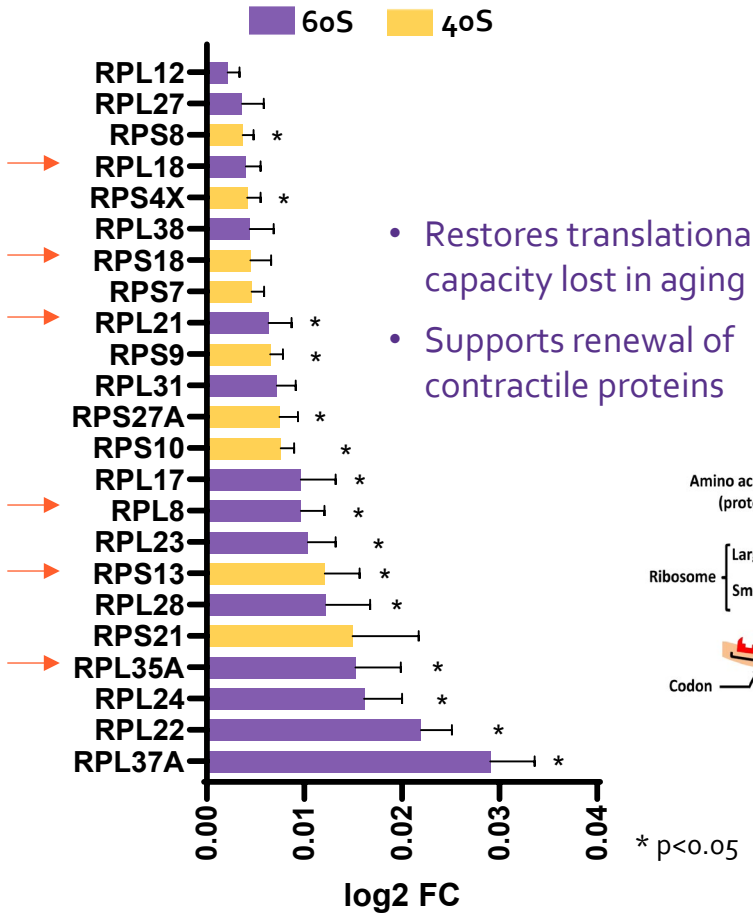
- **Ribosomes are the cell's protein-manufacturing machines — fewer ribosomal proteins means less capacity to build and replace muscle protein.**

Ribosomal protein abundance declines with age in human muscle



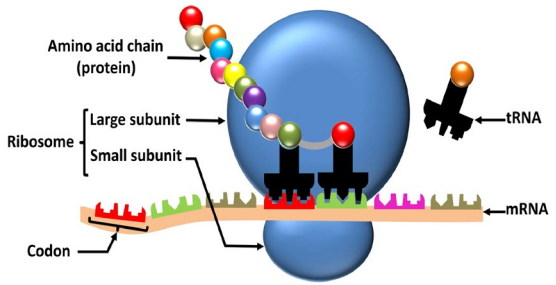
- Reflects reduced translational capacity — less new protein synthesis
- Impaired proteostasis allows damaged contractile proteins to accumulate

MF-300 restores large (60S) and small (40S) ribosomal proteins



* p<0.05

- Restores translational capacity lost in aging
- Supports renewal of contractile proteins

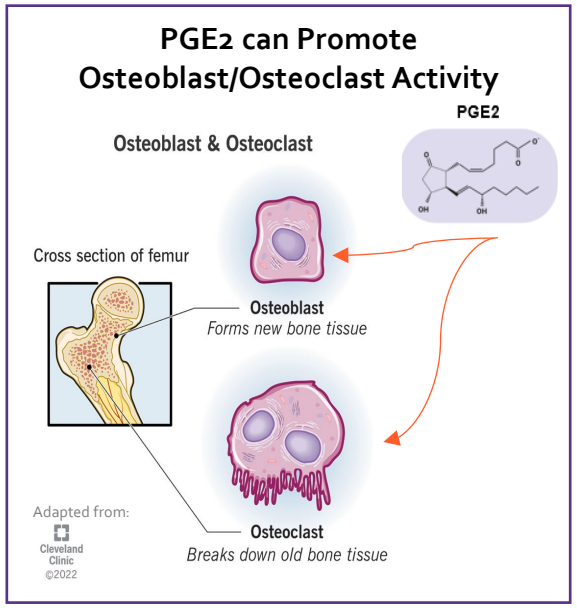


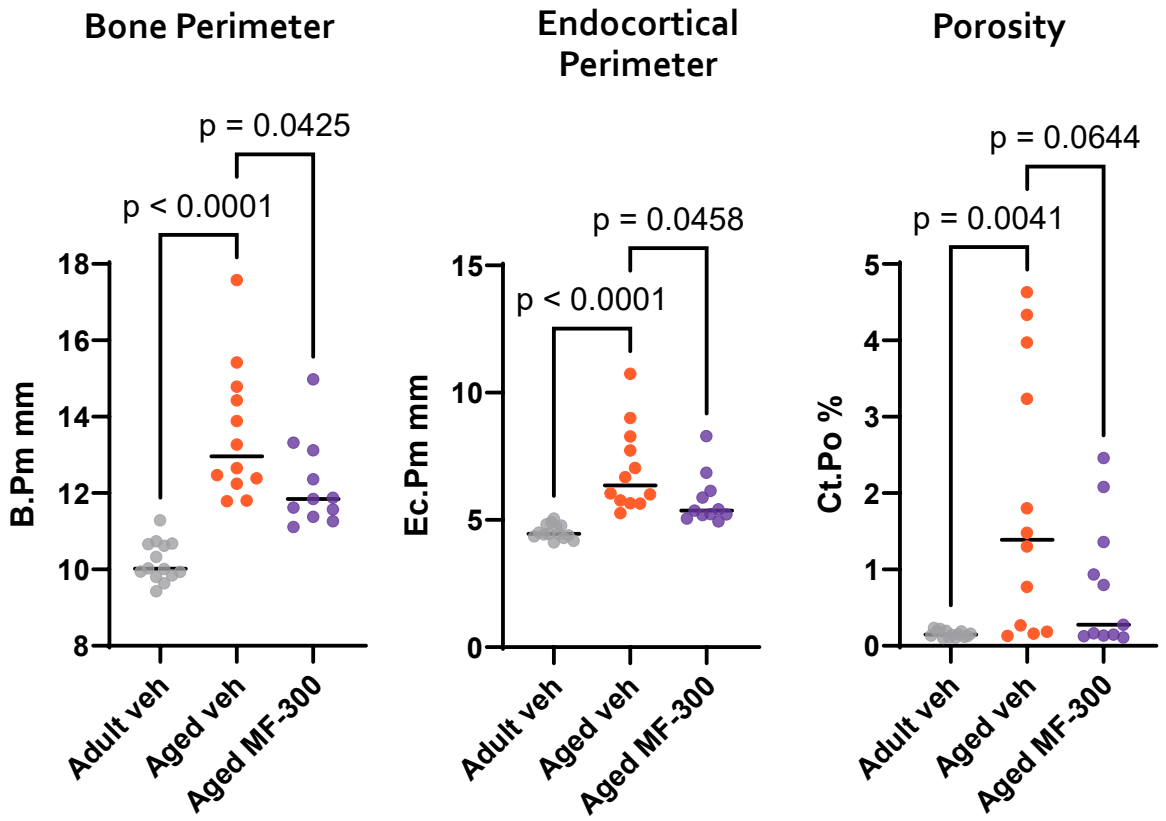
Ubaida-Mohien et al., *eLife*, 2019

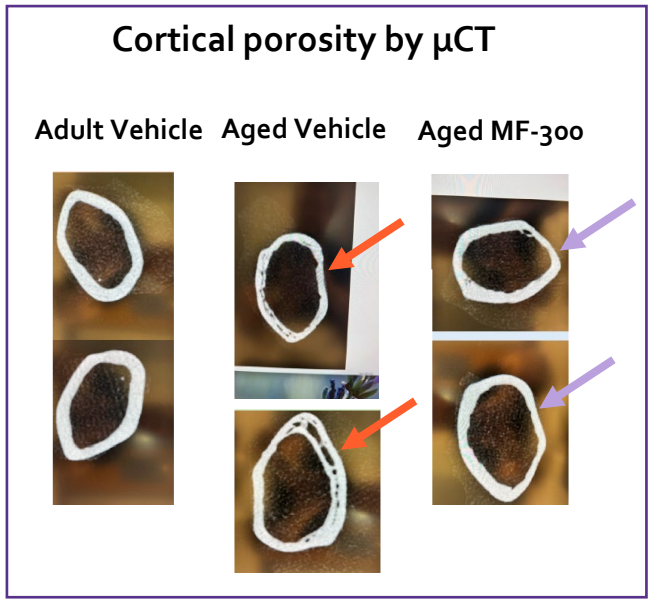
Arrows = aging-reduced ribosomal proteins restored by MF-300

MF-300 Slows Cortical Bone Aging — Extending PGE2 Benefit from Muscle to Bone

- Cortical bone grows more porous with age in rodents and humans — a driver of hip, wrist, and vertebral fractures
- PGE2 balances bone formation and resorption; MF-300 raises PGE2 to support remodeling
- In aged mice, MF-300 shifted bone perimeter and endocortical perimeter back toward young, with porosity trending lower







12 weeks MF-300 Oral Administration

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Phase 1 Results:

- Safety
- Pharmacokinetics and Pharmacodynamics
- Phase 2 Study Design & Endpoints
- Positive FDA Type C Meeting Overview

Phase 1 Clinical Study: Evaluating the Safety, Pharmacokinetics and Pharmacodynamics of MF-300 in Younger and Older Adults

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Design: Double-blind, randomized, placebo-controlled

Objectives:

- Assess safety and tolerability of MF-300
- Characterize MF-300 pharmacokinetics and pharmacodynamics (PGE2, PGE-MUM)

Populations:

- Younger adults ≥ 18 - ≤ 65 years; Healthy volunteers
- Older adults >65 - ≤75 years; Controlled chronic conditions and stable concomitant medications permitted

Single Ascending and Multiple Ascending Dose Cohorts:

- Single Ascending Dose (SAD): 5 dose levels (75–800 mg), older adults received 125 mg
- Multiple Ascending Dose (MAD): 3 dose levels (75, 125, 200 mg) administered once daily (QD) for 5 days, older adults received 200 mg

Part 1a SAD	Part 2 MAD
• 5 younger adult cohorts, 1 older adult cohort • N=8 per cohort (2 pbo, 6 MF-300) • Single dose • Doses: 75, 125, 250, 500, & 800mg	• 3 younger adult cohorts, 1 older adult cohort • N=10 per cohort (2 pbo, 8 MF-300) • QD dosing for 5 days • Doses: 75mg, 125mg, 200mg

[1] Older adults received MF-300 125mg in the SAD phase and MF-300 200mg in the MAD phase.

Phase 1 Clinical Success Criteria to Enable Phase 2b

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- **All predefined Phase 1 success criteria across Safety, PK, and PD were achieved**
- **Comparable clinical profile between younger and older adults**
- **Study results enable 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

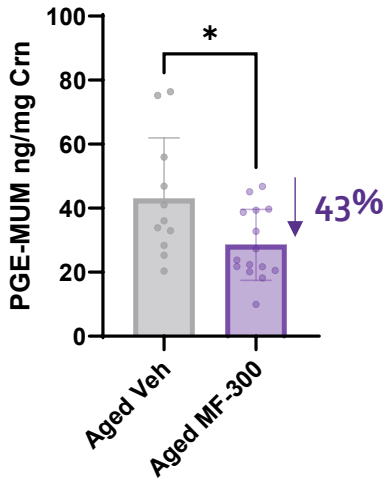
- ✓ Evidence of target engagement (15-PGDH) w/ substantial reductions in PGE_2 metabolites
- ✓ Proof of mechanism: Clear evidence of mechanism with dose-related increases in PGE2 levels
- ✓ Clear dose-response relationship defining therapeutic range, supportive of Phase 2b dose selection

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

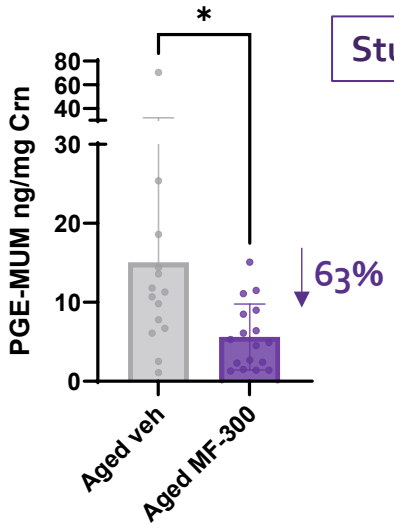


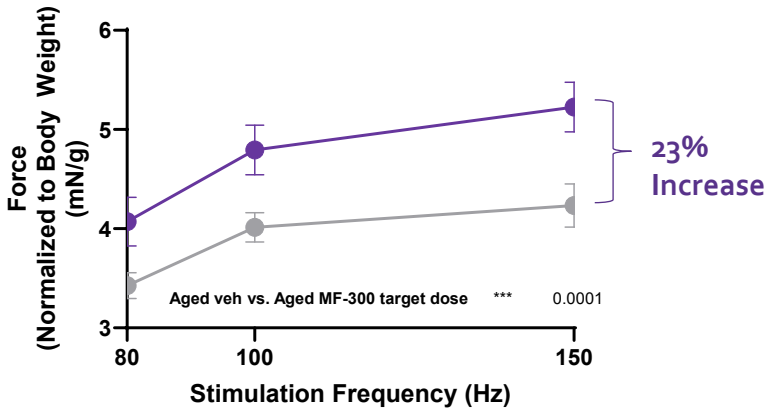
Vehicle
MF-300 target dose mg/kg

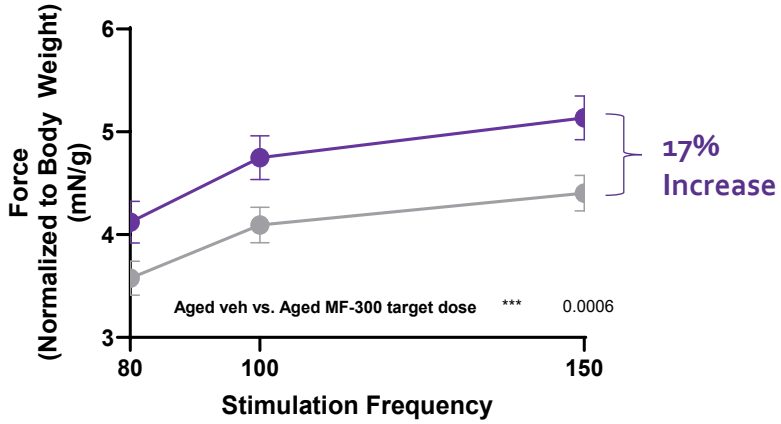
PGE-MUM
↓~50% average

Force
↑~20% average

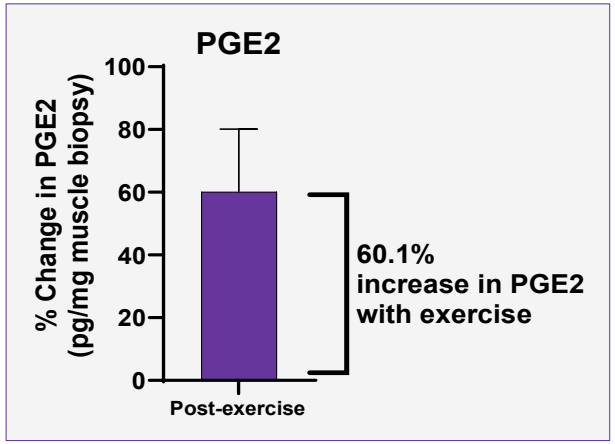
Study 2







PGE2 in human muscle



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

Target Engagement Biomarker

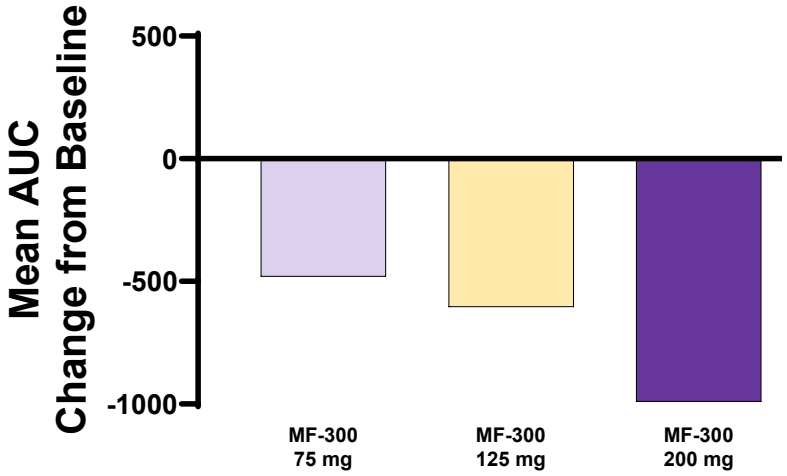
- ~50% reduction in PGE-MUM is correlated with
- ~20% improvement in muscle force

Biomarker Data Provides Proof of Mechanism for MF-300 in Younger Adults

- PGE-MUM Reductions Consistent with ~20% improvement in muscle force in sarcopenia mouse model
- PGE2 Increases consistent with that following eccentric exercise in humans (~60%)

Placebo-adjusted PGE-MUM Change from Baseline

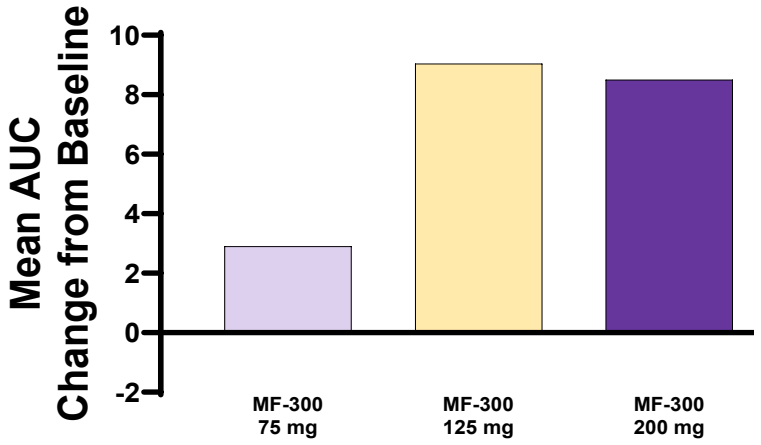
MF-300 (mg)	75	125	200
Placebo Adj. % Change	-64%	-64%	-83%*



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

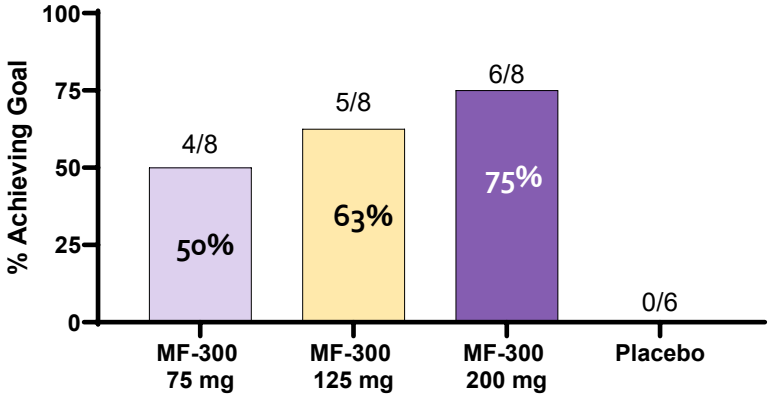
Placebo-adjusted PGE2 Change from Baseline

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.

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



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

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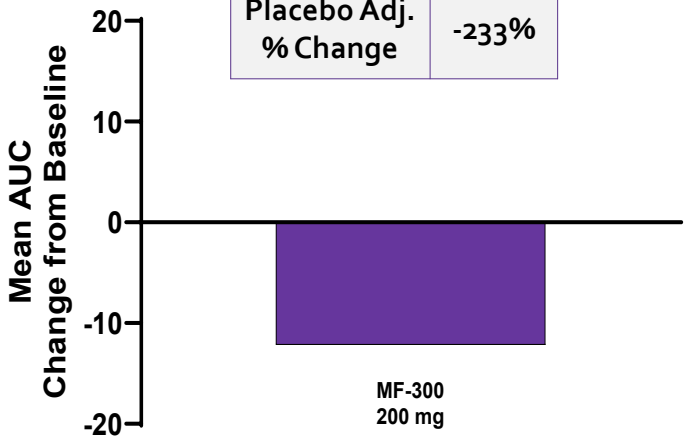
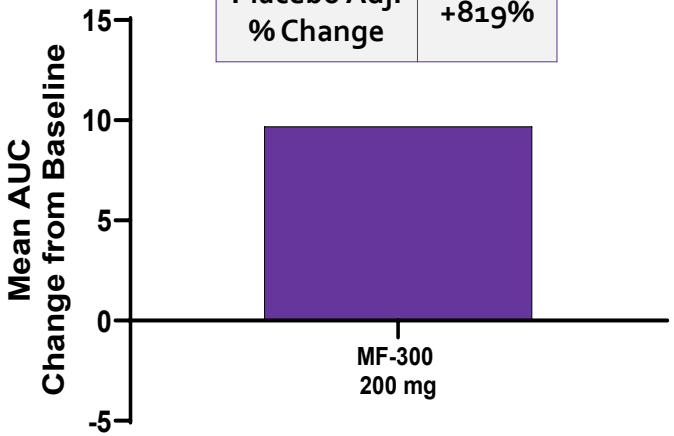
Placebo-adjusted PGE-MUM Change from Baseline

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

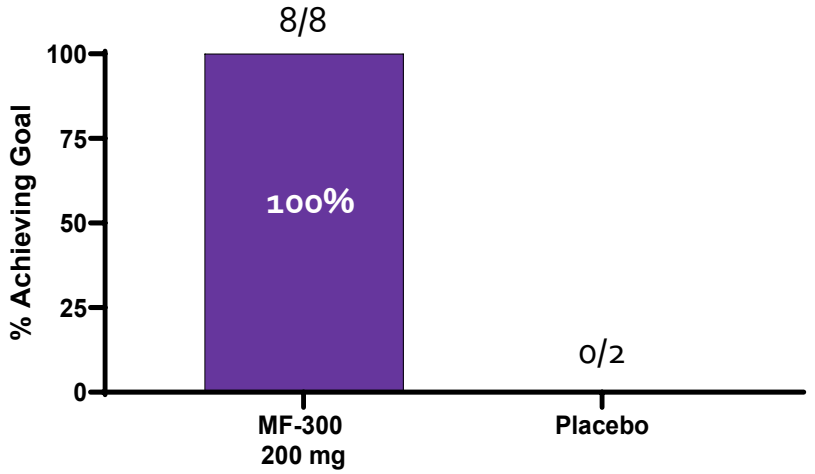


Placebo-adjusted PGE2 Change from Baseline

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



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



Two-Part Phase 2 Program

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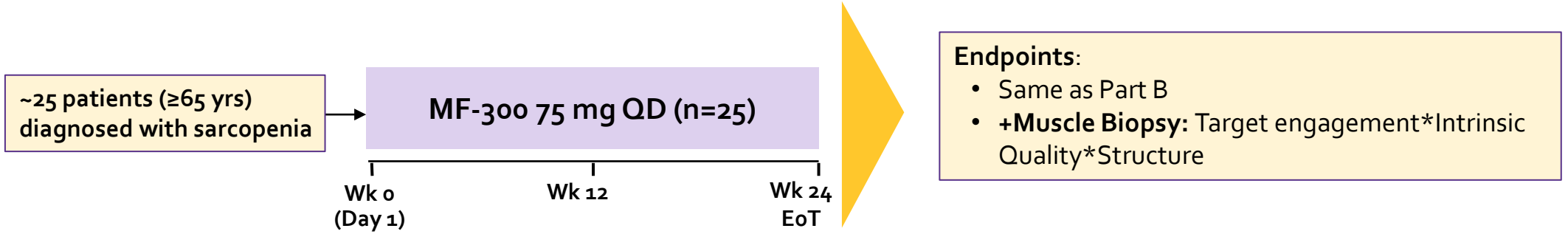
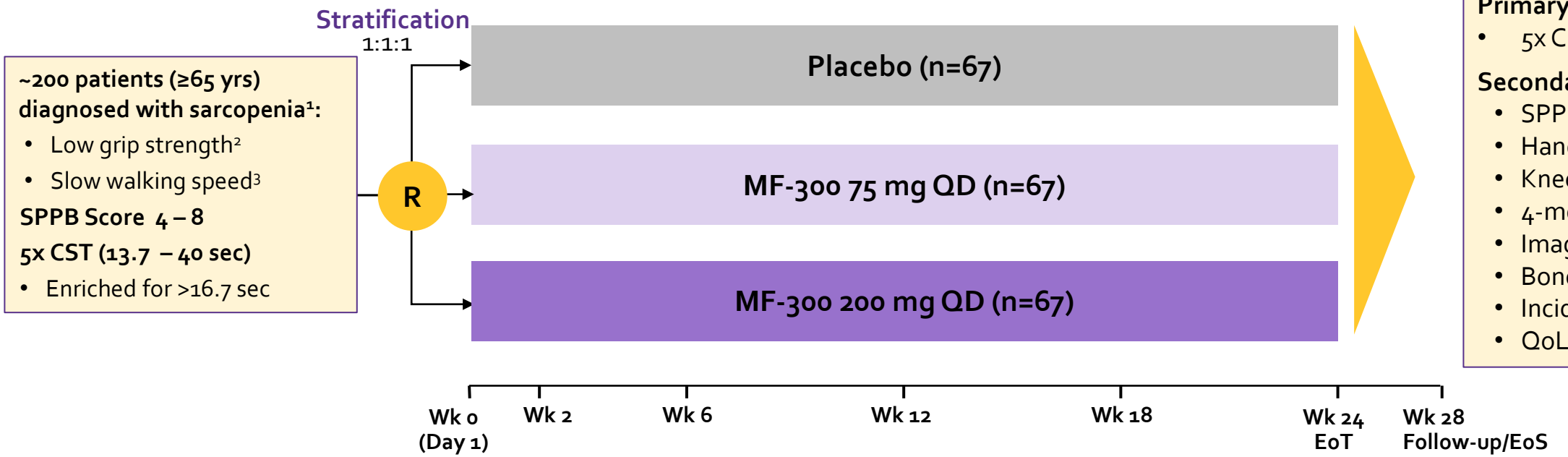
Part A: Open-label (Early data informs fine-tuning of Part B execution, enrollment criteria and powering assumptions)



Endpoints:
- Same as Part B
- **+Muscle Biopsy:** Target engagement*Intrinsic Quality*Structure

Part B: Double-blind Randomized Placebo Controlled



Primary Endpoint:
- 5x Chair Stand Test

Secondary Endpoints:
- SPPB
- Hand grip strength
- Knee extension
- 4-meter gait speed
- Imaging (DXA, CT)
- Bone biomarkers
- Incidence of falls
- QoL Measures

EoT=end of treatment; EoS=end of study; R=randomization; SPPB=Short Physical Performance Battery; Wk=week

[1] Saropenia Definitions and Outcomes Consortium, Bhasin S, et al. J Gerontol A Biol Sci Med Sci. 2023; [2] <35.5 kg for men, <20 kg for women; [3] <0.8 m/s

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**
- **The Phase 2b study design was endorsed,** including FDA agreement to the patient population, primary and secondary efficacy endpoints, treatment duration and dosing regimen of MF-300
- **FDA agreed that the efficacy endpoints evaluated in the Phase 2b study will inform Phase 3 endpoint selection**
- **FDA supports pursuing Fast Track Designation,** signaling that they consider Sarcopenia a serious condition and that MF-300 has the potential to address an unmet need

Strategic Implications

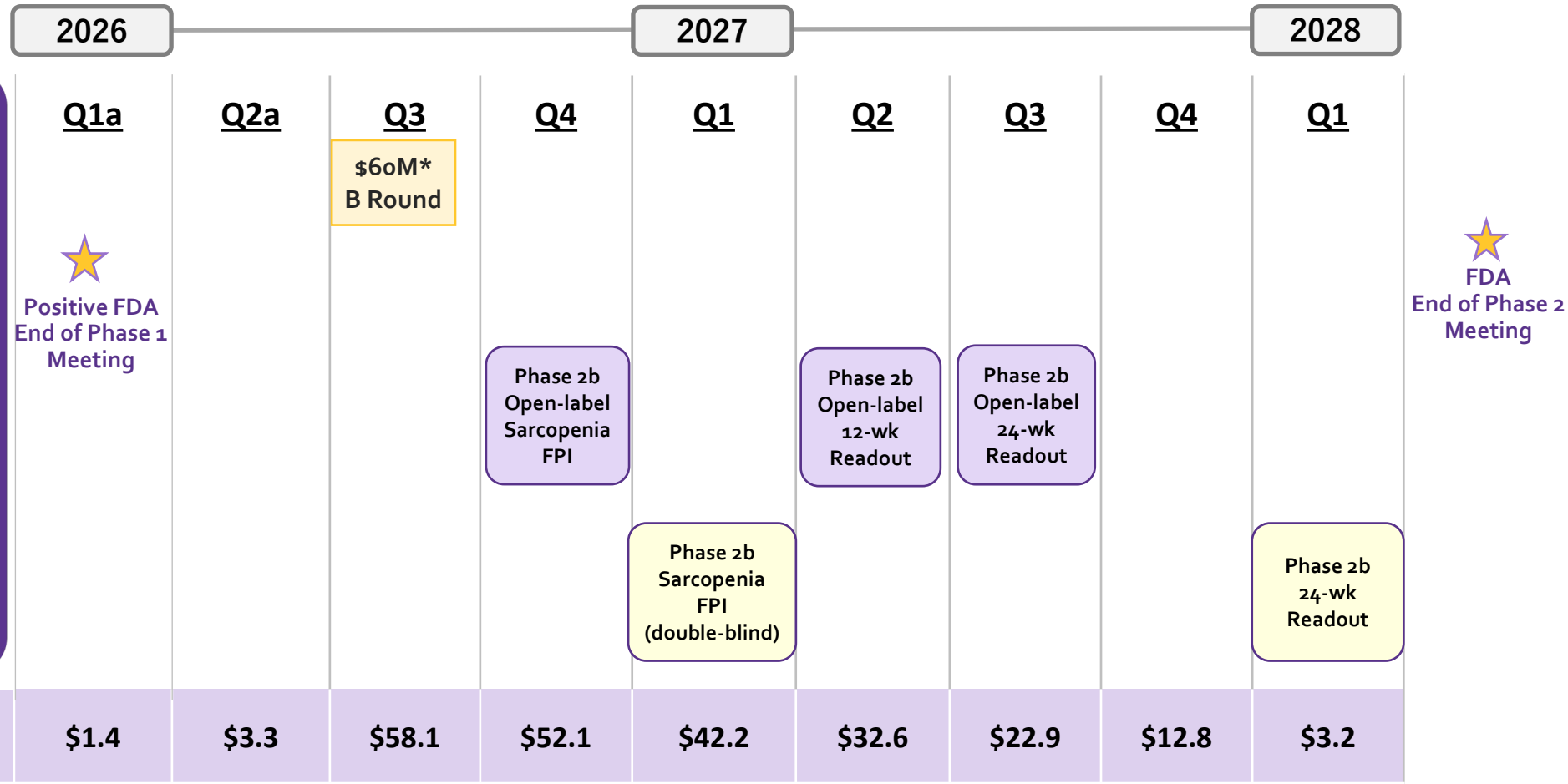
- Supports advancement of MF-300 to a Phase 2b study
- Phase 3 endpoint strategy is conditionally endorsed – regulatory risk around endpoints is reduced
- Fast Track, if accepted, will allow greater access to FDA during development and enable priority review, potentially accelerating development timelines

$60M Series B Achieves Phase 2 Readouts – Multiple Value Inflection Points

Epirium Bio

$60M Series B* Achieves Phase 2 Readouts:

- Phase 2b Readouts
  - – Starting Q2 '27
  - – Final Topline Q1 '28
- End of Phase 2 FDA meeting – Q2 '28



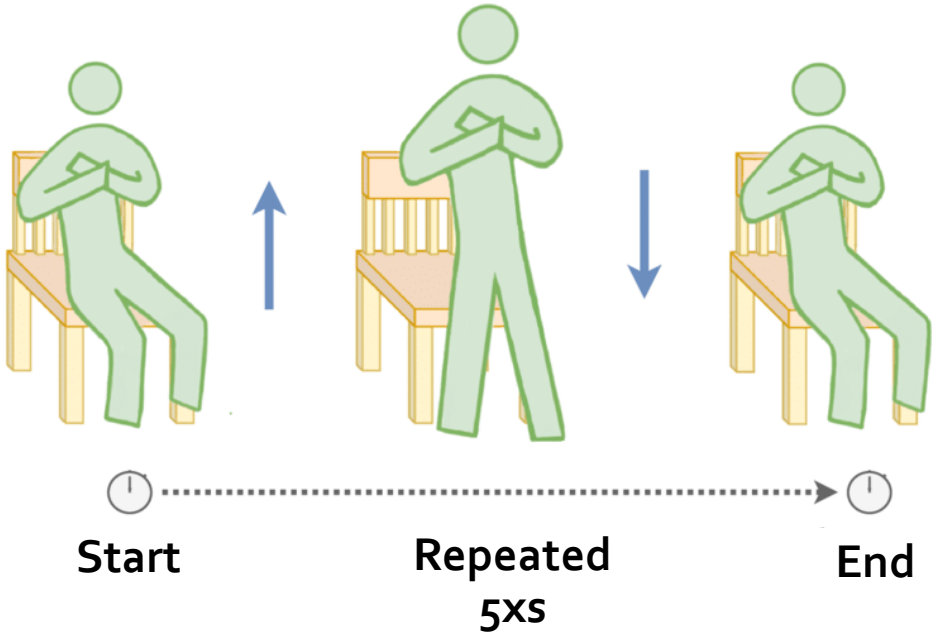
Addendum :

- Alignment with the FDA on Sarcopenia Trial Endpoints Prior to Phase 3
- Epirium SDC Members

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).

Endpoint Strategy

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Four step plan confirming established endpoints are "fit-for-purpose" for Phase 3 — Targeted evidence from Phase 2b, leveraging what already exists.

01 Define What Matters

A qualitative literature review builds a conceptual model of **what matters most to sarcopenia patients' health** — the foundation the trial endpoints are measured against.

Underway

02 Gap Assessment

Do the chosen endpoints measure what matters to patients? Psychometric **gap analysis reviews the existing reliability and validity evidence** for each endpoint and pinpoints the focused set of gaps to close for Phase 3.

- Forms basis for **analysis plan**

Underway

03 Phase 2b Analysis

A pre-specified, FDA-agreed Phase 2b analysis produces the needed evidence, establishing each **endpoint's reliability, validity** and how much change is meaningful to patients (**MCID***).

Q1 2028

04 Lock in FDA Agreement

The completed evidence package submitted to FDA at the EOP2 meeting to align on Phase 3 endpoints before the pivotal trial — removing a major source of risk.

Q2 2028

PRIMARY ENDPOINT

5× Chair Stand Test

SECONDARY ENDPOINTS

SPPB | Handgrip Strength | PROMIS-PF PRO

MCID: minimally clinically important difference

Endpoint Strategy: Leadership & Timeline

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LED BY RECOGNIZED REGULATORY EXPERTS

- **Stacie Hudgens - Lead**
  Chief Scientific & Strategy Officer
  20+ years in psychometrics and FDA submissions; served on the FDA's Study Endpoints & Label Development panel.

- **Dr. Naomi Lowy**
  Former FDA Deputy Director, General Endocrinology
  The division's former regulatory lead on sarcopenia and cancer cachexia; advises the endpoint strategy.

TIMELINE & NEXT STEPS

Now → end 2026
Build plan: literature review, gap analysis, Phase 2b analysis plan

End 2026
Submit plan: Alignment with FDA on endpoint strategy before Phase 2b

Q1 27 – Q1 28
Phase 2b study conduct; generate final evidence under agreed plan (measurement–validity white paper)

Q2 2028
Secure FDA agreement on Phase 3 endpoint(s) at EOP2 meeting

Phase 3 → NDA
Endpoints and MCID confirmed; complete COA evidence dossier filed with the NDA

HOW THE FDA DECIDES

The Division of Clinical Outcome Assessment (DCOA) judges each endpoint against clearly defined criteria. As these are **well-established endpoints**, the goal is **fit-for-purpose alignment for this specific context of use** — a defined, finite evidence set. This pathway compiles that evidence into a Dossier filed with the NDA, initiating this work now, with early FDA feedback and Phase 2b data, substantially reduces regulatory risk at filing.

MCID: minimally clinically important difference

Epirium Sarcopenia Clinical Development Advisors

Epirium Bio

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

Se-Jin Lee, MD, PhD

Presidential Distinguished Professor

University of Connecticut School of Medicine

Professor, The Jackson Laboratory.

Studying the mechanism of action of myostatin and how its activity is regulated.