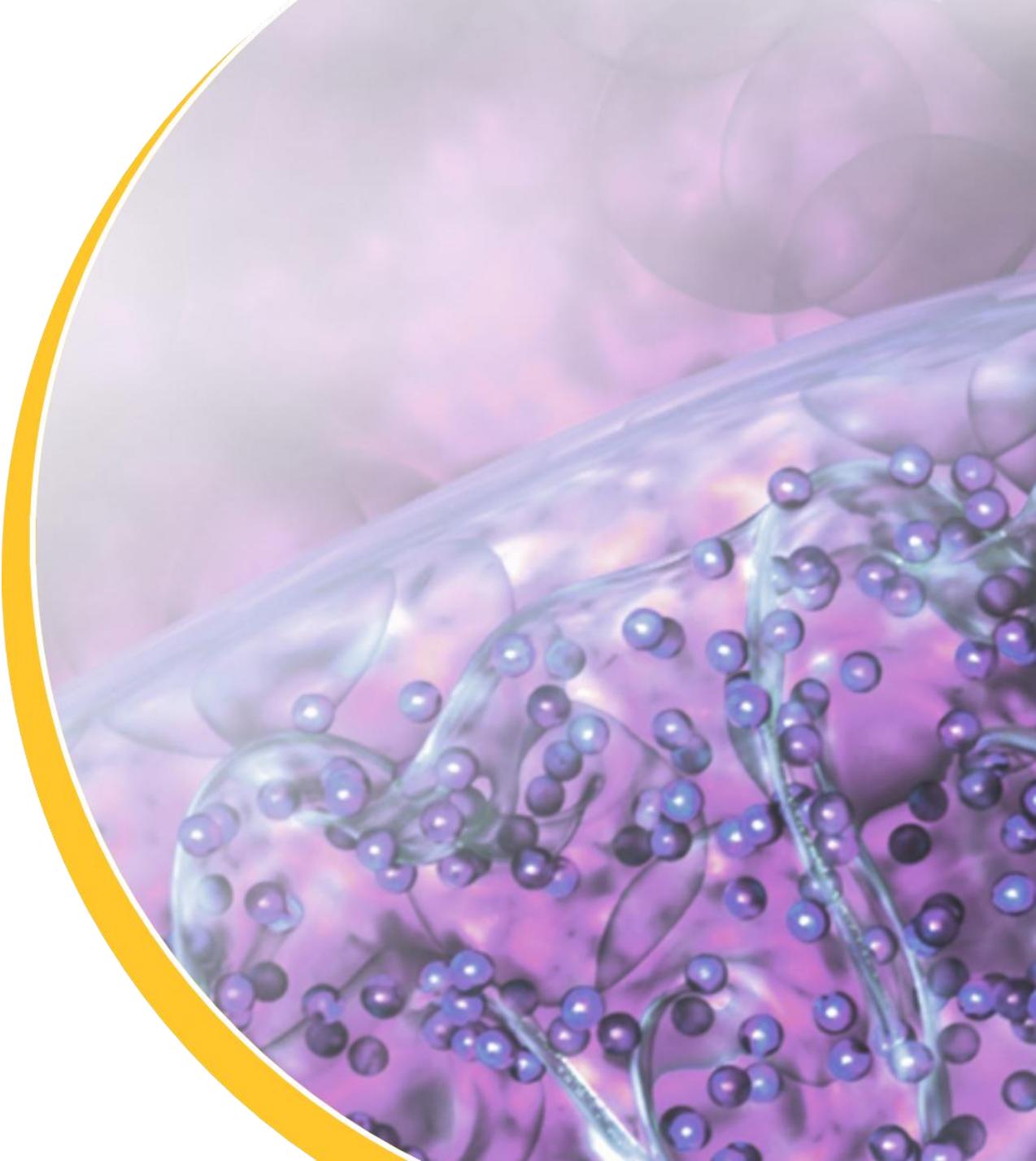




Oral 15-PGDH Inhibitor Platform:
Leveraging PGE₂ Signaling To Treat
Sarcopenia, Neuromuscular &
Inflammatory Diseases (IBD):

- 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 (acq. Sanofi)

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

Cadence Pharm. (acq. 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) 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



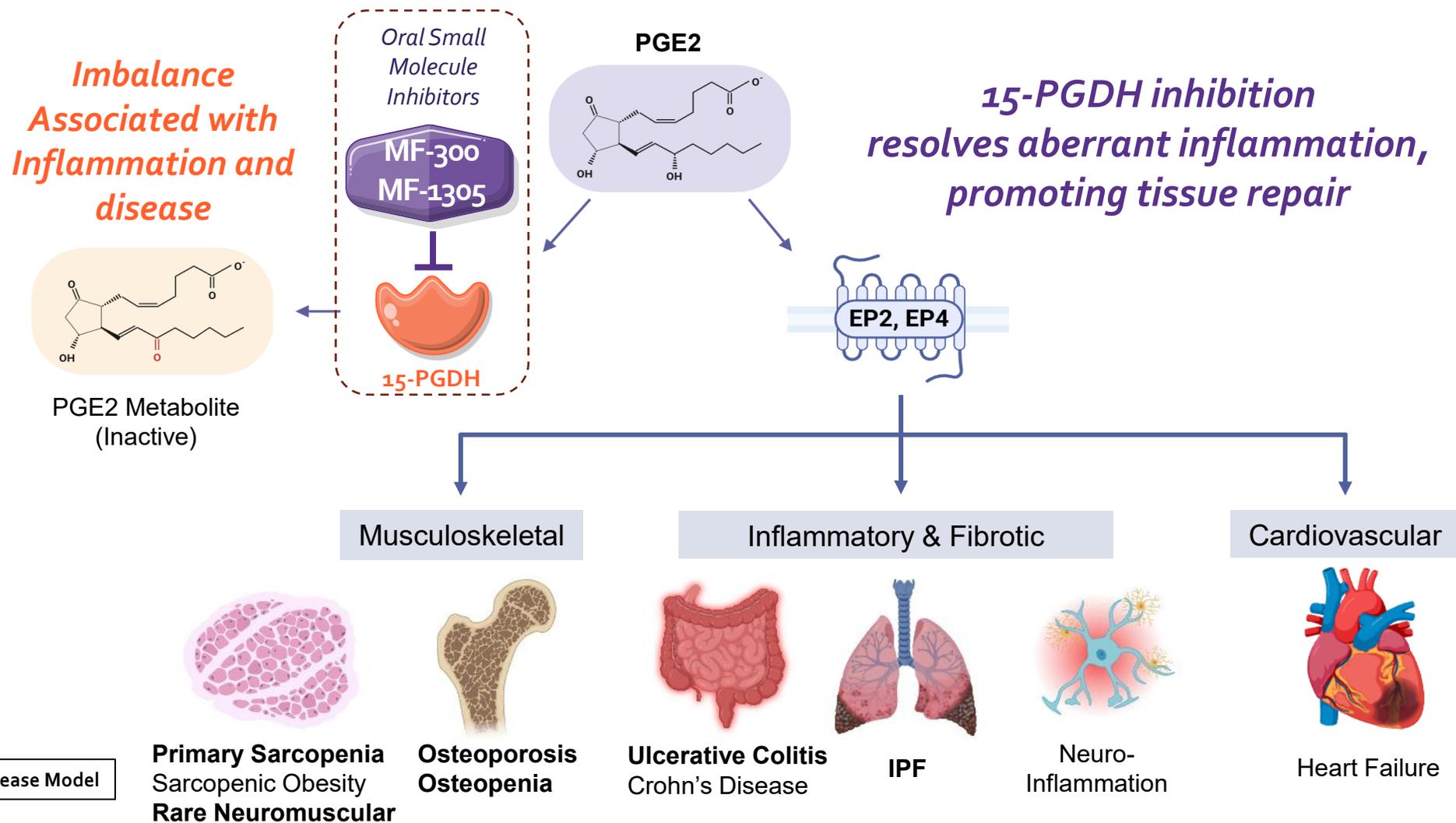
Roger Fielding, Ph.D. Professor of Medicine

Researcher studying the underlying mechanisms contributing to the age-associated decline in skeletal muscle mass

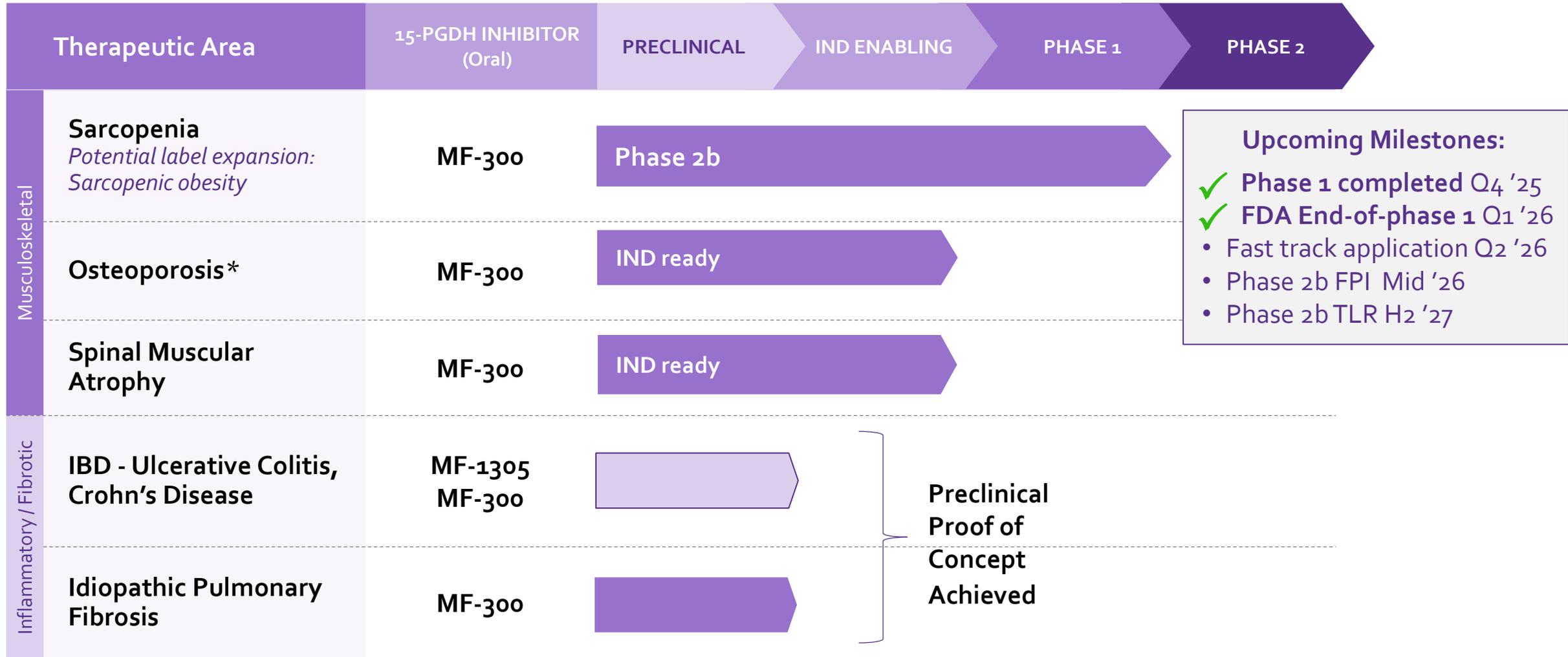
Published over 200 per-reviewed papers and 8,000 citations

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

Inhibiting 15-PGDH to leverage the potential of PGE₂ signaling in restoring tissue homeostasis: rebalancing inflammation, stimulating regeneration, reducing fibrosis



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



*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



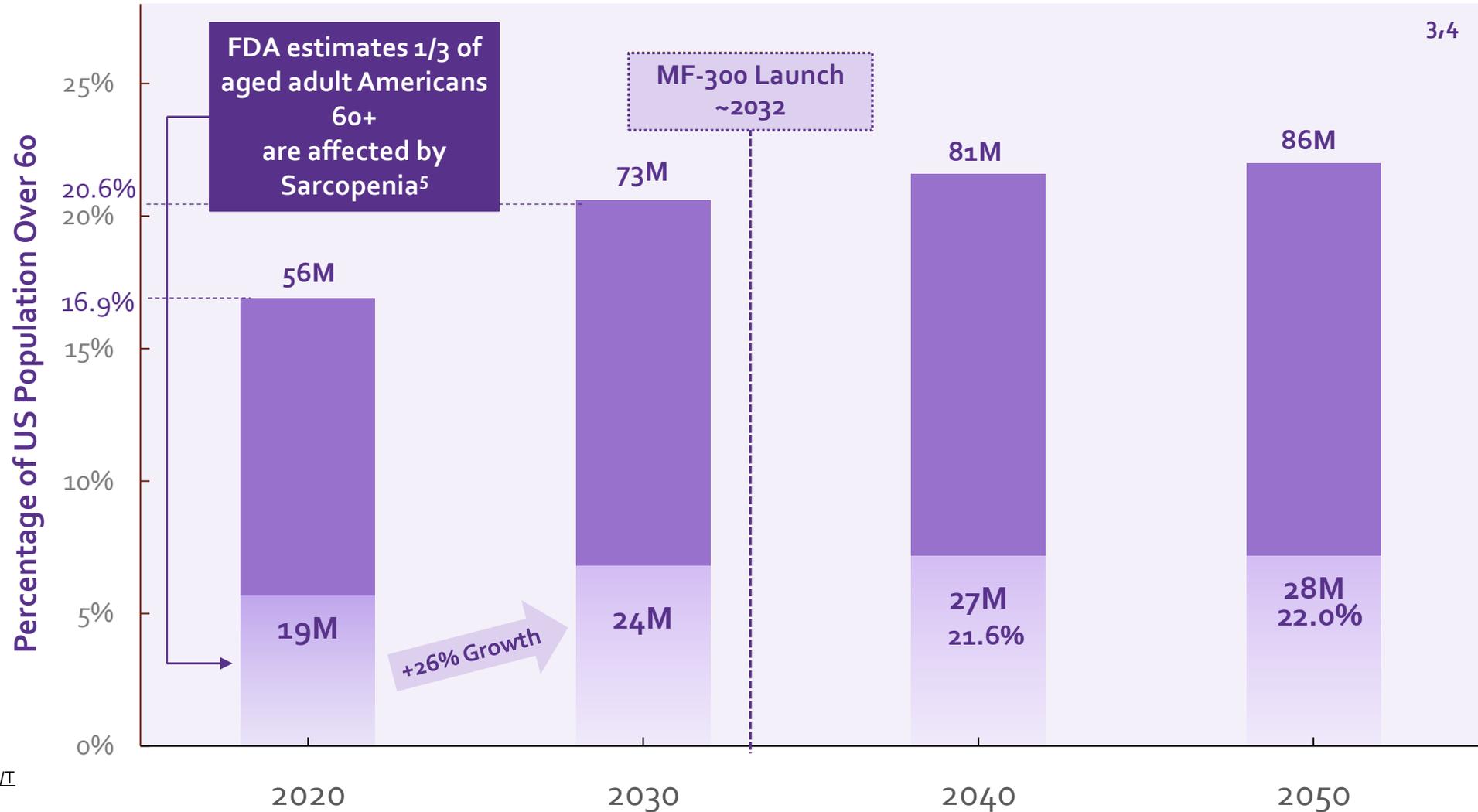
Sarcopenia: Large and Growing Unmet Medical Need w/ No FDA Approved Therapy

Current U.S. Healthcare Sarcopenia Spending Estimated >\$40 Billion Annually¹

Dependence
Increased risk losing independence

Falls
Increased Morbidity & Mortality²

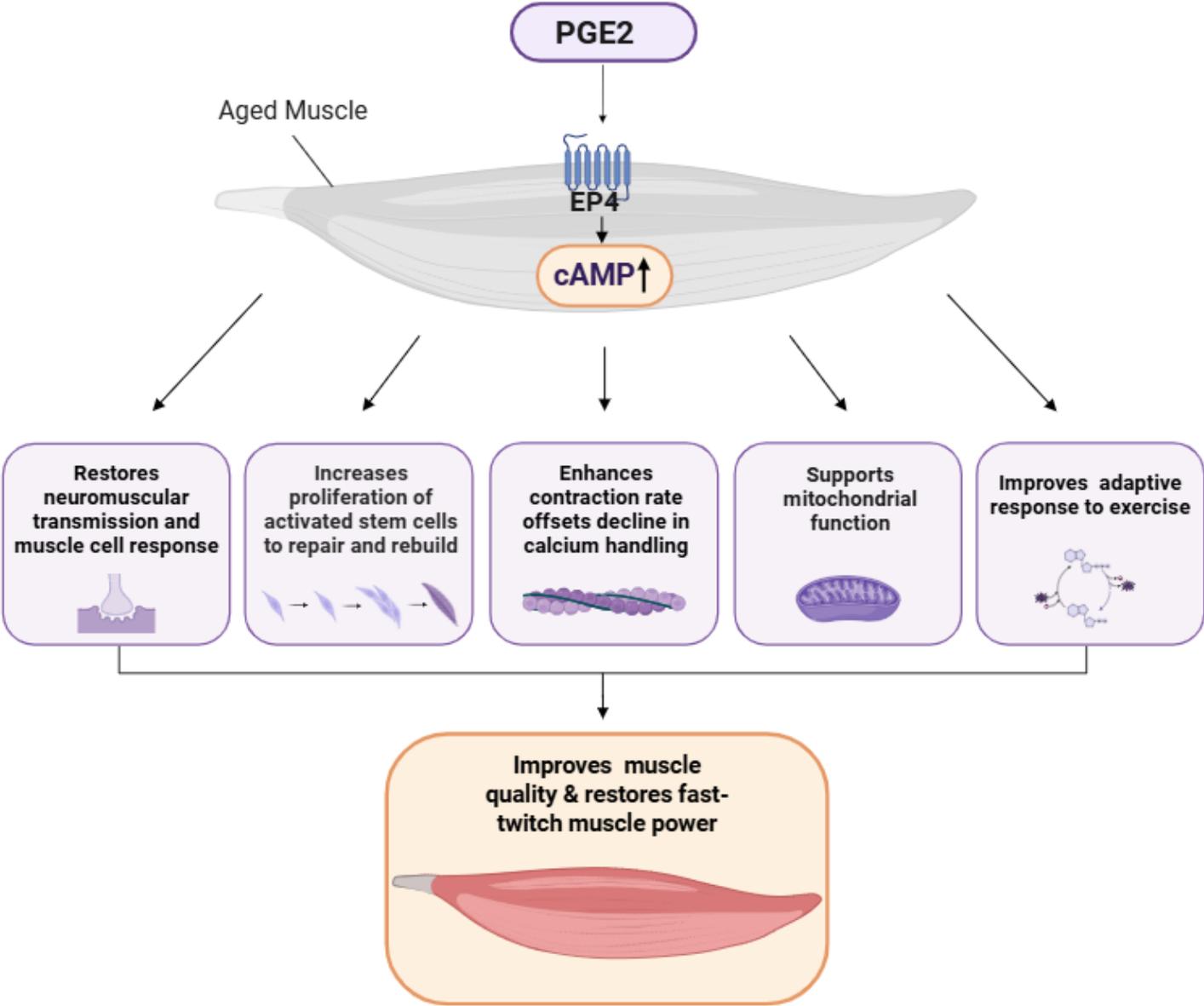
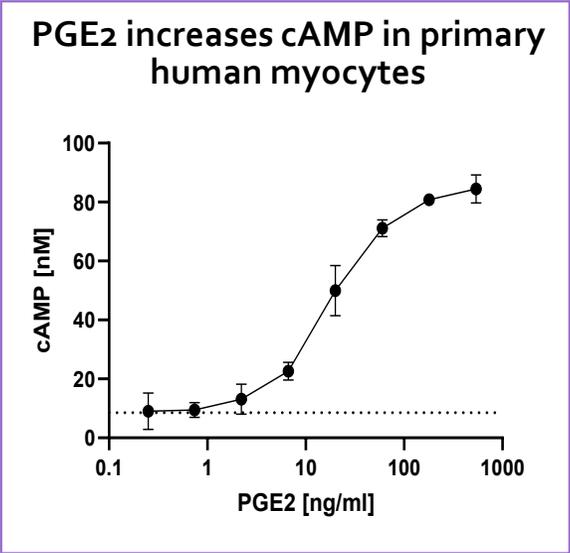
Mortality
Increased risk of death²



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%20ofda/published/THe-Voice-of-the-Patient--Sarcopenia.pdf>

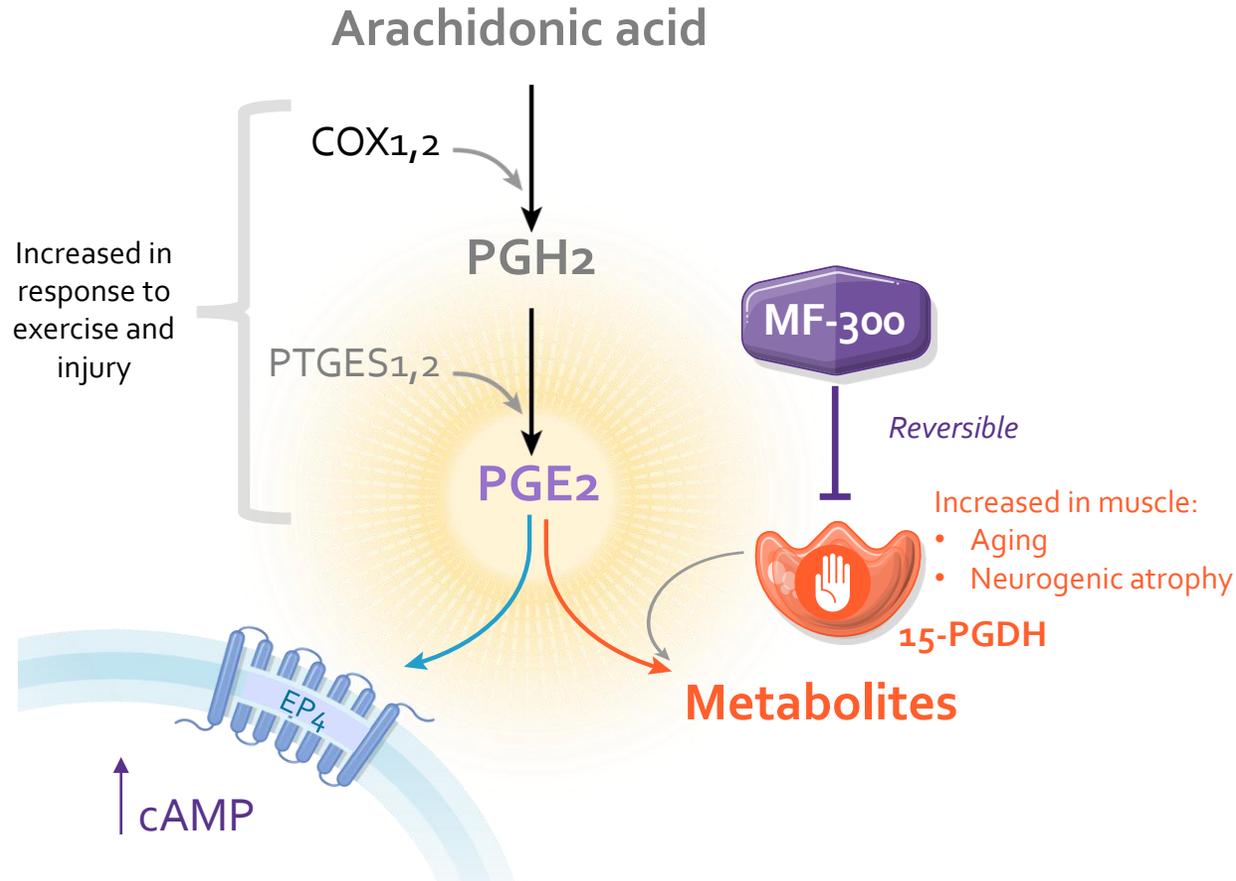
PGE2 Increases cAMP Resulting in Improved Muscle Quality



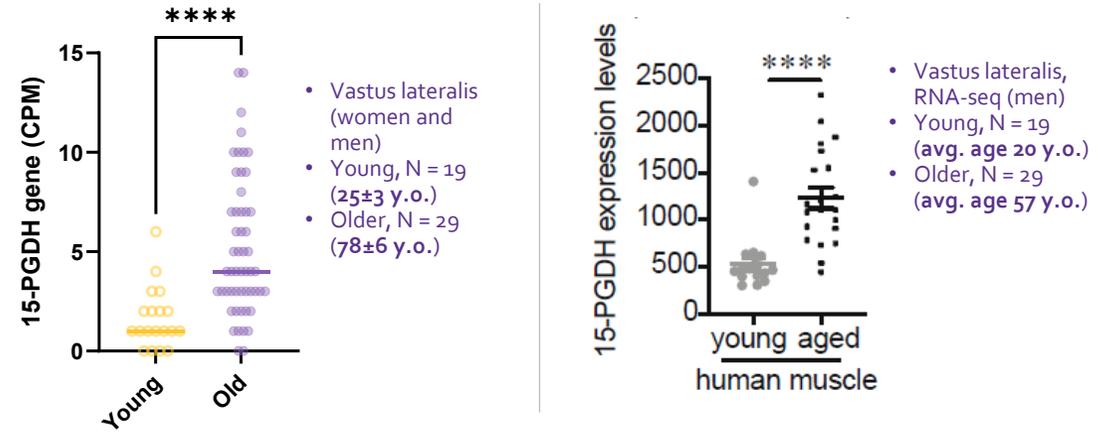
Berdeaux et al., 2012
Ho et al., 2017
Palla et al., 2021
Bakooshli et al., 2023
Epirium unpublished data

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

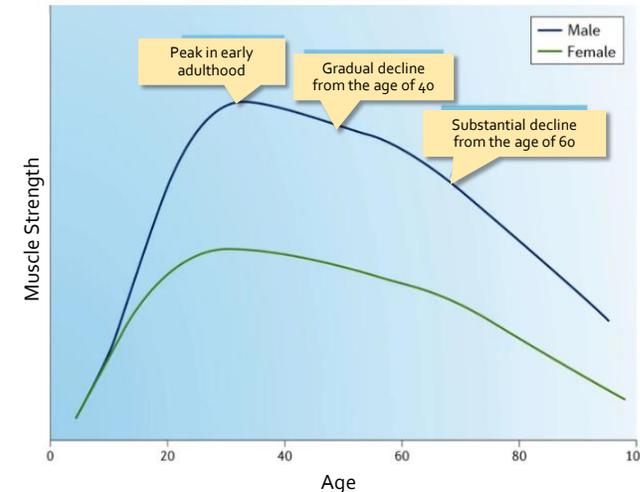
15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2



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



Grip strength, a predictor of sarcopenia risk, declines with age⁵

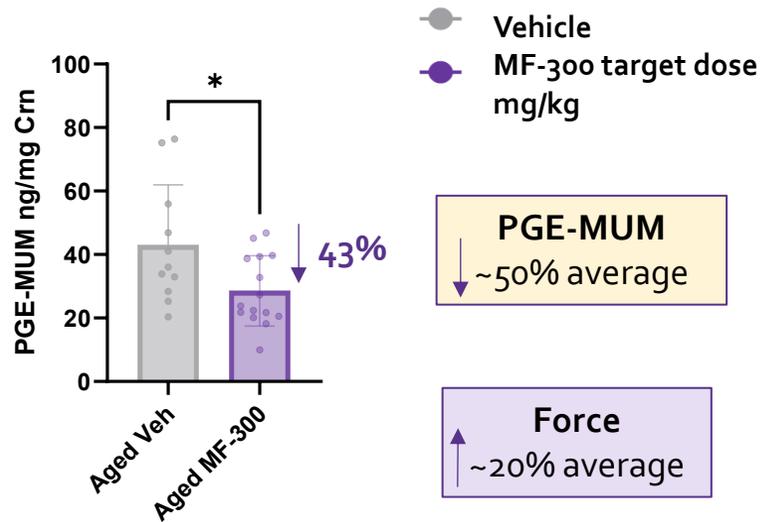


³ GEO167186, ⁴ Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), ⁵ Dennison et al., *Nat Rev Rheum* 2017

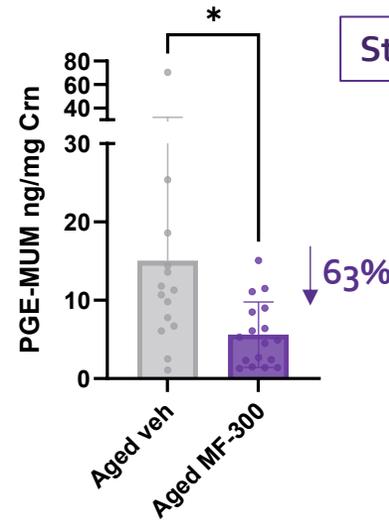
Preclinical Sarcopenia Studies

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

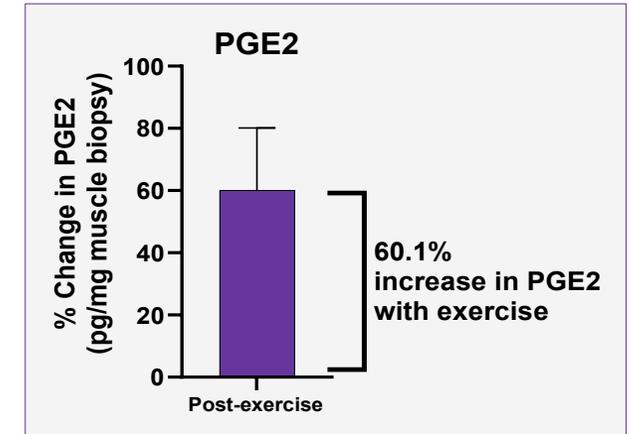
Study 1



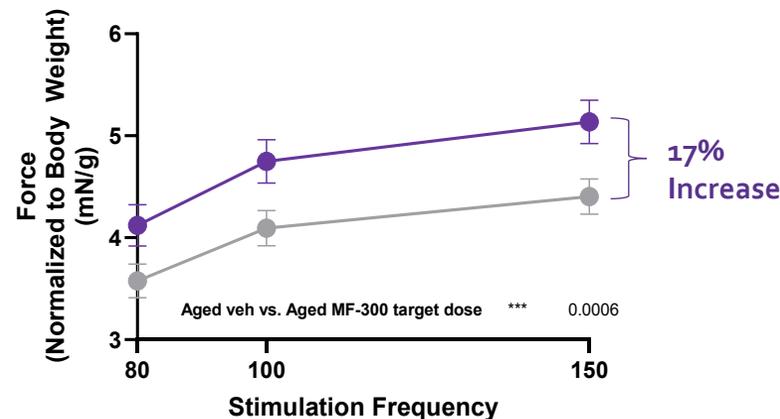
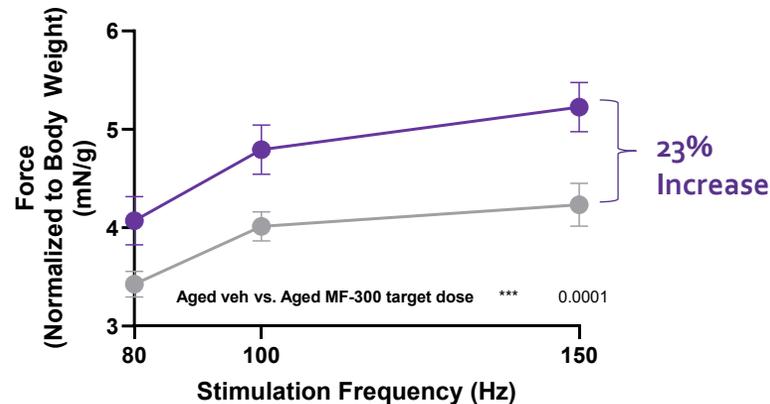
Study 2



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

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 $\geq 18 - \leq 65$ years of age & Healthy elderly cohort $>65 - \leq 75$ 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

- 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 $\geq 50\%$ 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'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

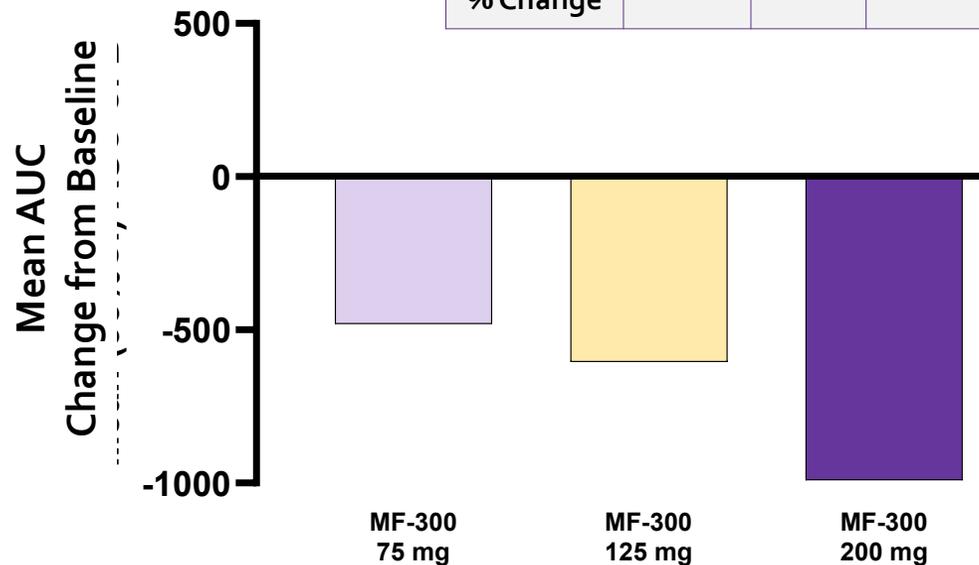
No additional monitoring required beyond standard Phase 2b assessment

Increased PGE₂ Levels with MF-300 Demonstrates Proof of Mechanism

- 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)

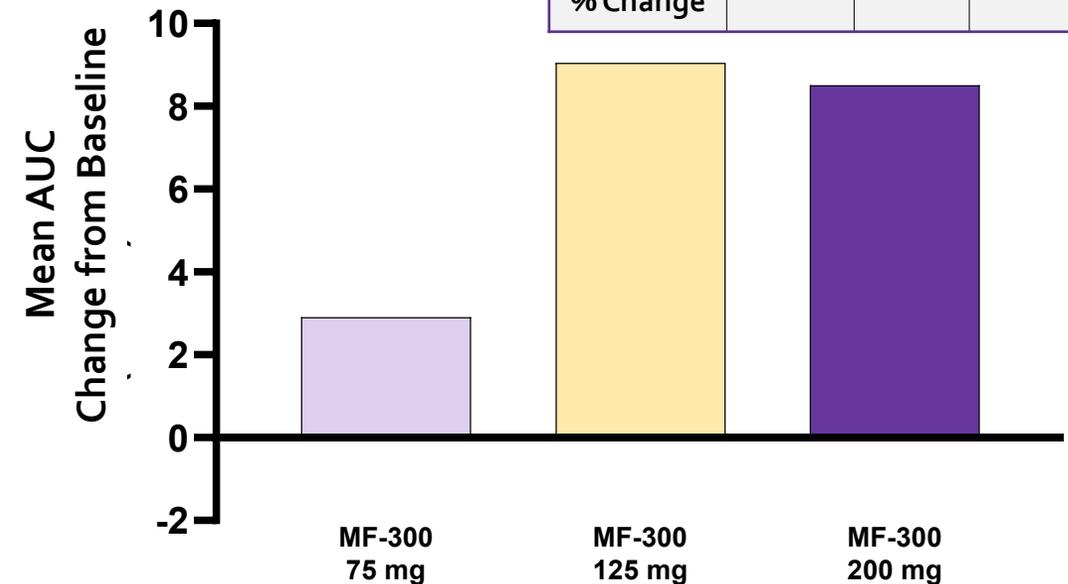
MF-300 (mg)	75	125	200
Placebo Adj. % Change	-64%	-64%	-83%*



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

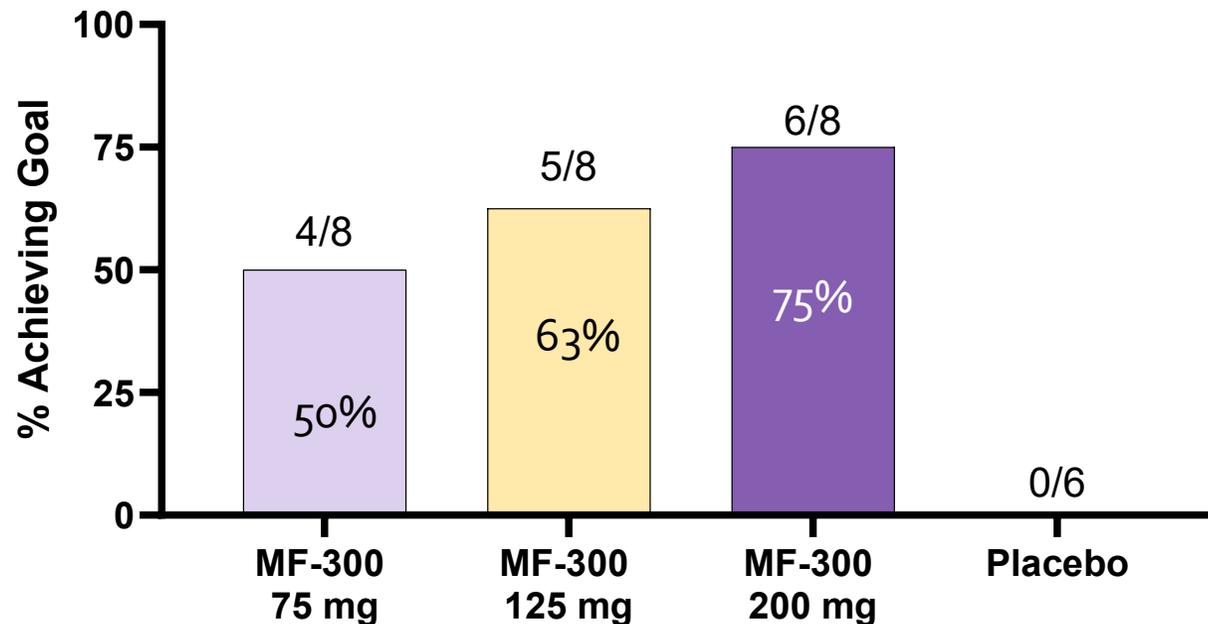
Placebo-adjusted PGE₂ Change from Baseline (95% CI)

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.

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



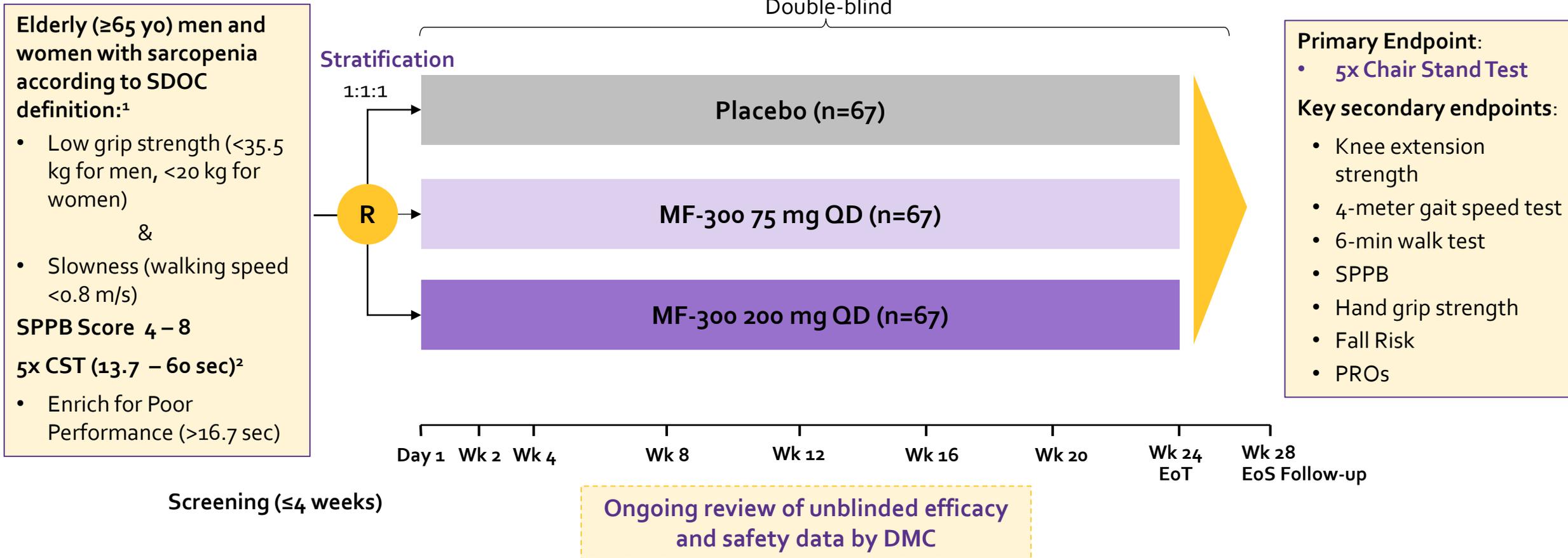
Rationale for targets:

- ~Targeted % reduction in PGE-MUM is associated with ~20% improvement in muscle force
- ~60% increase in muscle following eccentric exercise in humans¹

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

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

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



*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.

- **Accepted proxy measure of lower limb power and strength**

- Endorsed by World Health Organization (WHO) ICOPE¹ & EWGSOP²

- **Strong predictor of clinical outcomes**

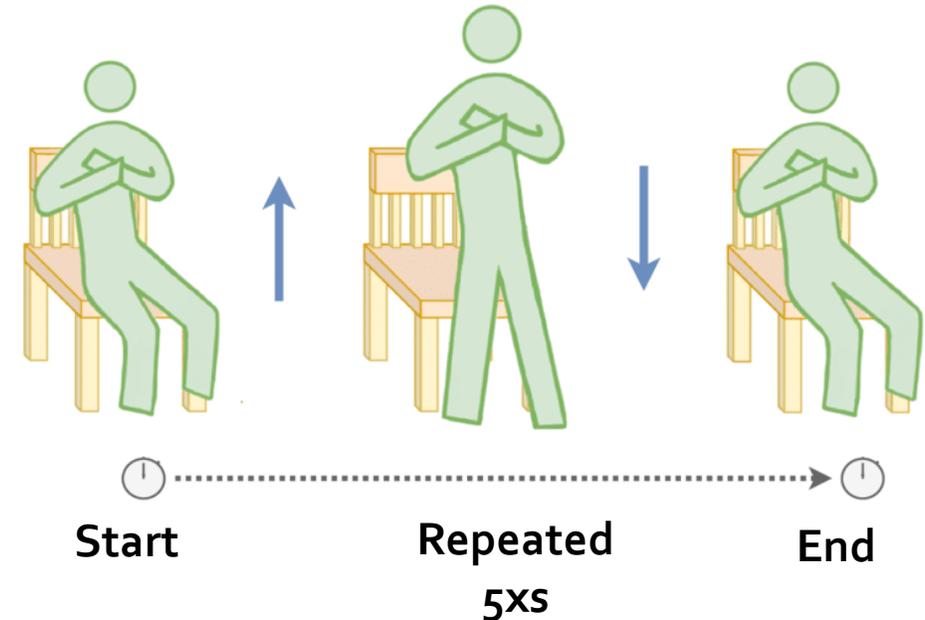
- Activities of daily living
- Fall Risk
- All-Cause Mortality

- **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

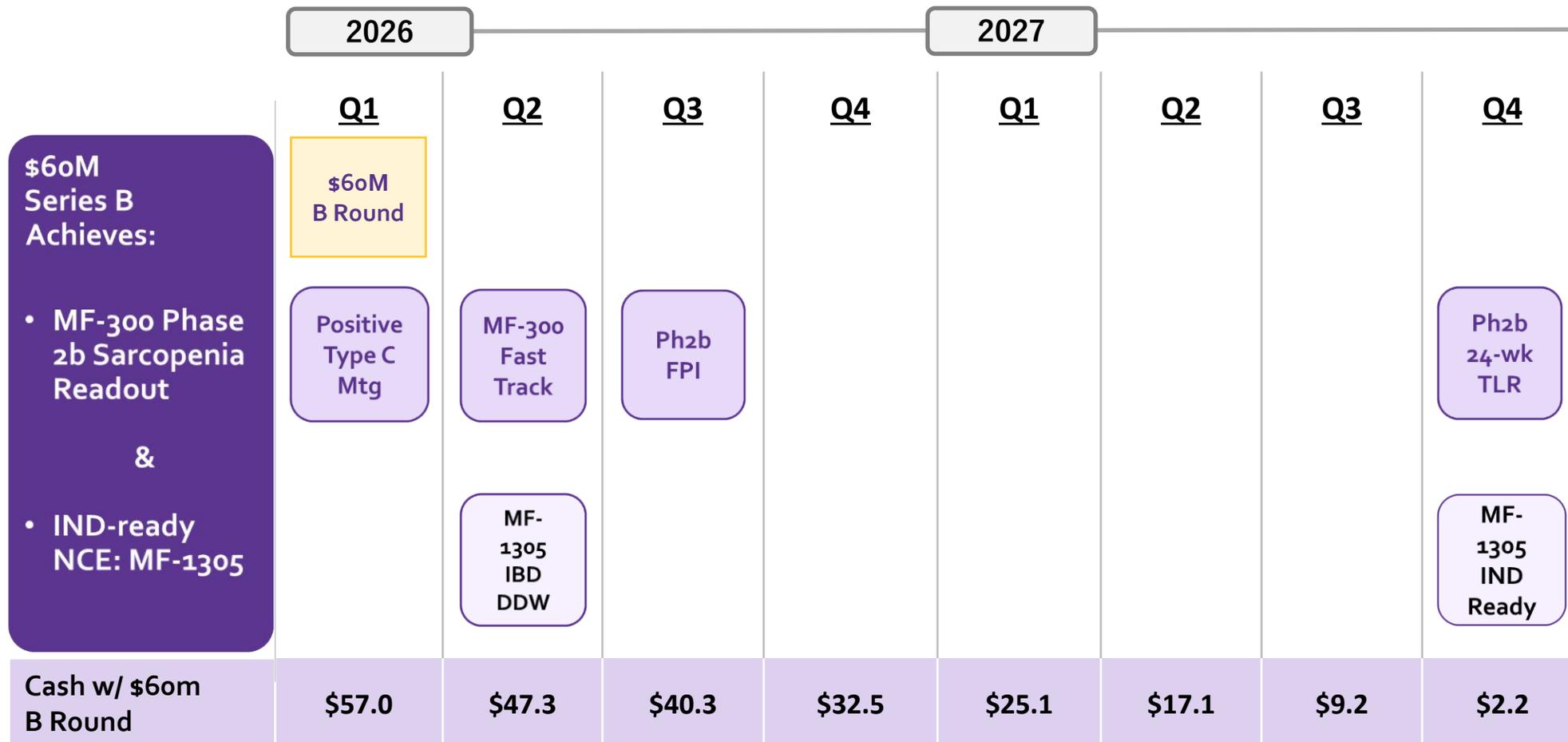
5xs Chair Stand Test



1. ICOPE=Integrated Care for Older People ([9789240103726-eng.pdf](https://www.who.int/publications/i/item/9789240103726-eng))

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

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



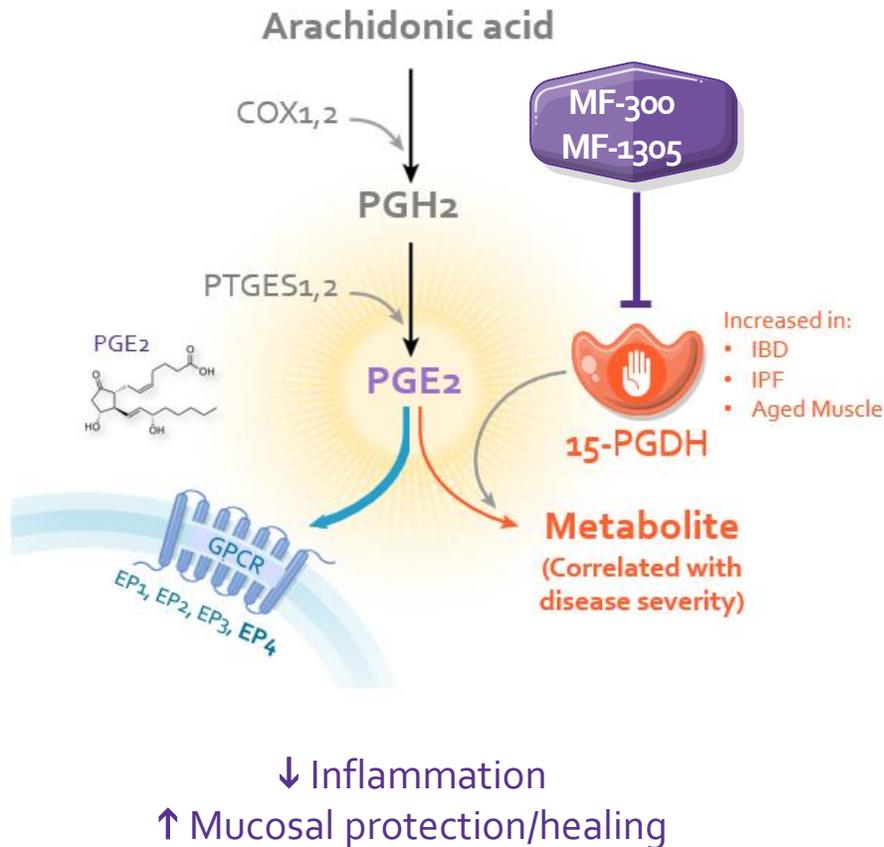
Additional \$25M (\$85M raise) enables Phase 3 CMC commencement bringing forward MF-300 Commercial Launch 6 months to 1H 2032

Positive IBD Results: MF-1305 DSS Mouse IBD Colitis Study

- Supportive Scientific Rationale
- Detailed Treatment Study Results

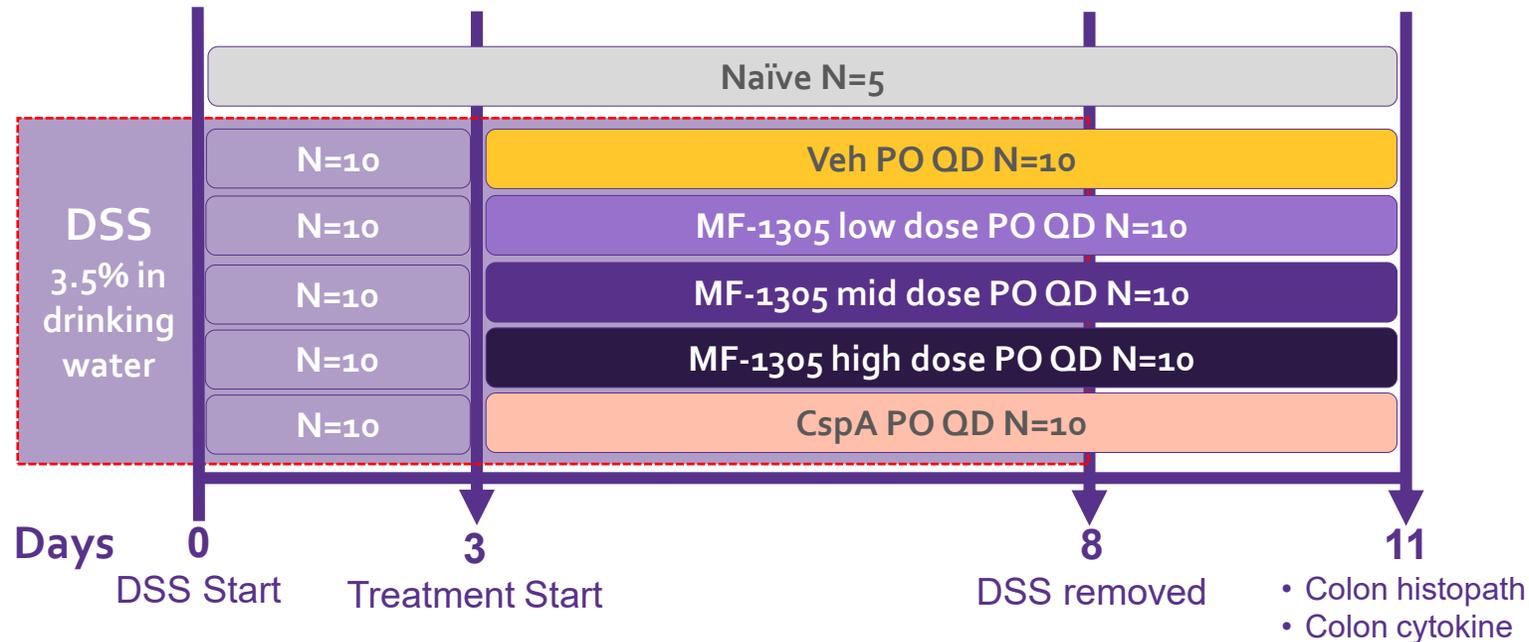
Inhibiting 15-PGDH with an Oral Small Molecule to Increase Physiological PGE₂: Proven Mechanistic Rationale for the Treatment of IBD

The PGE₂/EP₄ axis improves outcomes in DSS colitis models



Intervention / genetic model	Species & colitis model	Key outcomes	Reference
SW033291 (15-PGDH inhibitor, IP)	Mouse, DSS colitis	<ul style="list-style-type: none"> • Reduced % ulcerated colon area • Improved disease activity • Reduced pro-inflammatory cytokines • Increased crypt cell proliferation 	Zhang et al., 2015
HW201877 (15-PGDH inhibitor, PO)	Mouse, DSS colitis	<ul style="list-style-type: none"> • Improved DAI • Improved colon length • Improved histological measures 	Li et al., 2025
Hpgd knockout (15-PGDH gene)	Mouse, DSS colitis including older mice	<ul style="list-style-type: none"> • Minimize weight loss • Improved colon length & histology scores 	Zhang et al., 2015; Ho et al., 2022
AGN205203 (EP ₄ agonist)	Mouse, DSS (and DSS+indomethacin) colitis	<ul style="list-style-type: none"> • Improved DAI • Improved histology: preserved epithelium, reduced epithelial apoptosis, preserved goblet cells, enhanced epithelial regeneration 	Jiang et al., 2007
ONO-AE1-329 (EP ₄ agonist)	Rat & Mouse DSS colitis	<ul style="list-style-type: none"> • Reduced erosion/ulceration • Suppressed mucosal damage and inflammation • EP₄ KO & EP₄ antagonist worsened colitis 	Kabashima et al. (JCI) 2002; Nitta et al. 2002
KAG-308 (EP ₄ agonist)	Mouse, DSS colitis	<ul style="list-style-type: none"> • Suppressed DSS colitis onset • Promoted histological mucosal healing • Reduced TNFα production • EP₄ antagonist increased mortality 	Watanabe et al., 2015
PGE₂ (Exogenous)	Mouse, DSS colitis	<ul style="list-style-type: none"> • Alleviated mucosal injury • Promoted epithelial protection/healing 	Peng et al. 2017

- Mouse strain: C57Bl/6
- Sex/Age: Female/10-12 weeks



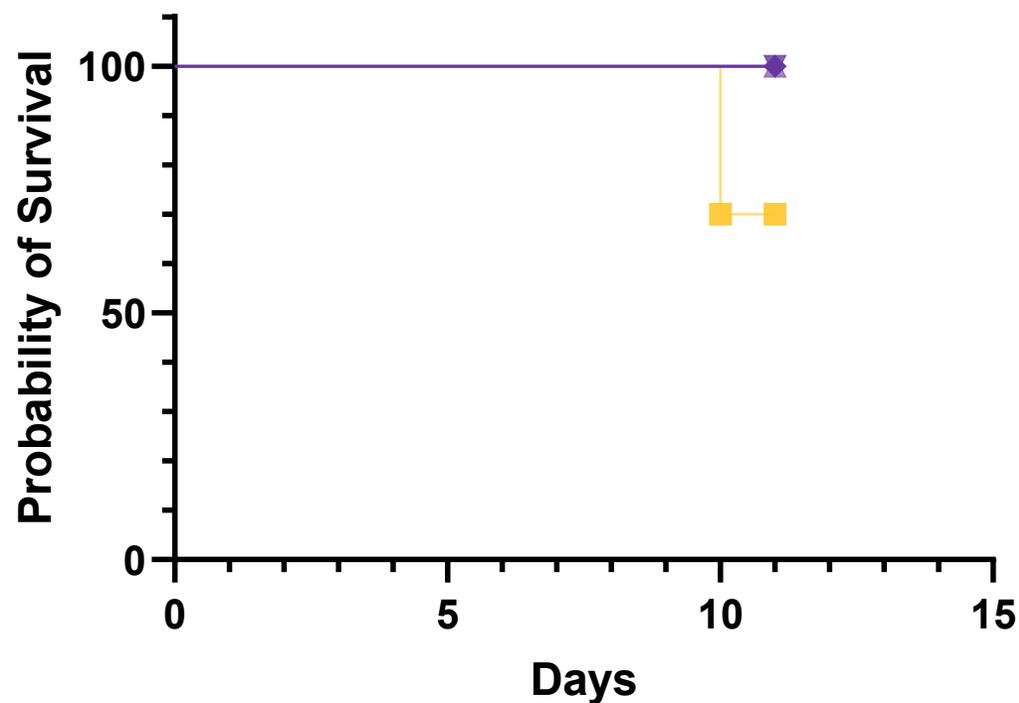
In life:

- Disease Activity Index (daily)
 - Body weight
 - Fecal blood
 - Stool consistency

Endpoints:

- Colon
 - Cytokines
 - Histology

Survival proportions: Survival of DSS



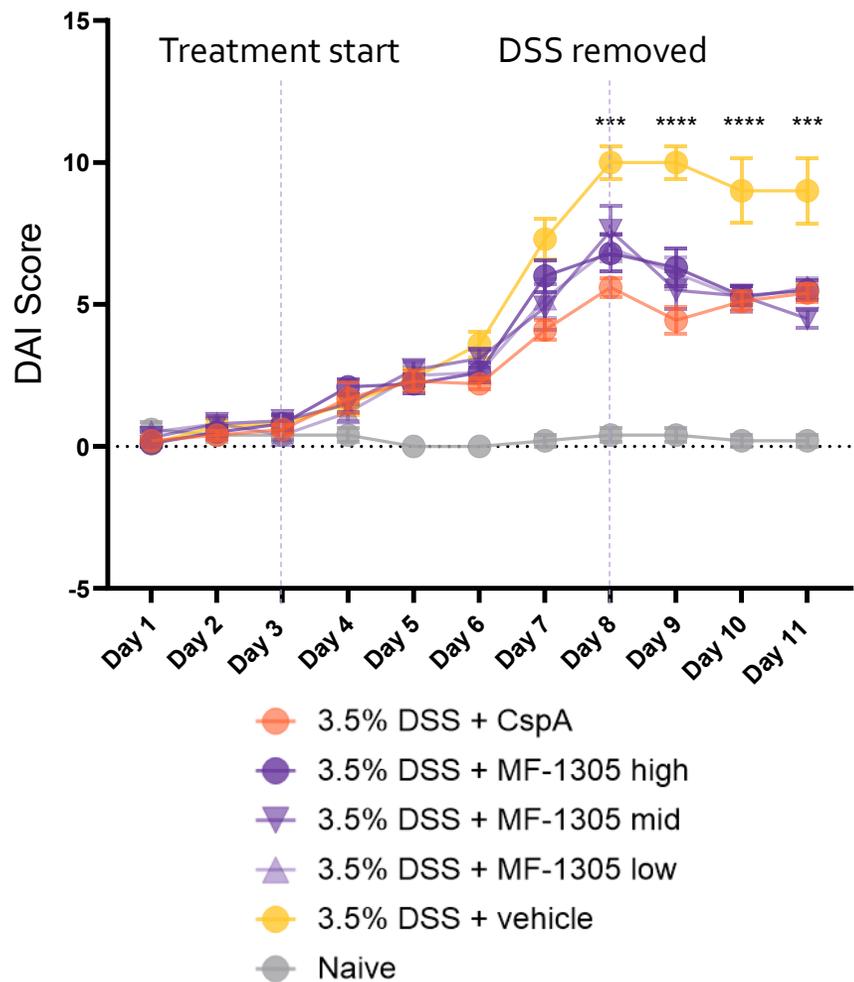
- ▲ DSS MF-1305
- ▼ DSS MF-1305
- ◆ DSS MF-1305
- DSS Veh

Log-rank (Mantel-Cox) test	
P value	0.0235
P value summary	*
Are the survival curves sig different?	Yes

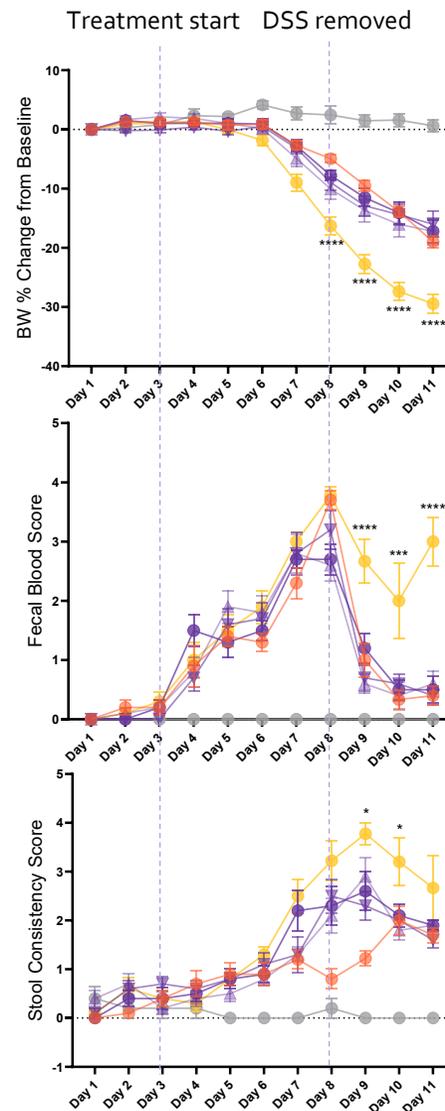
N = 3 animals from the DSS Veh group were euthanized on Day 10.
 Naïve and DSS CspA group, not included in survival analysis – both groups 100% survival.

MF-1305 Significantly Improved Disease Activity Index (DAI) & Survival

MF-1305 improved DAI



MF-1305 improved each composite score of the DAI



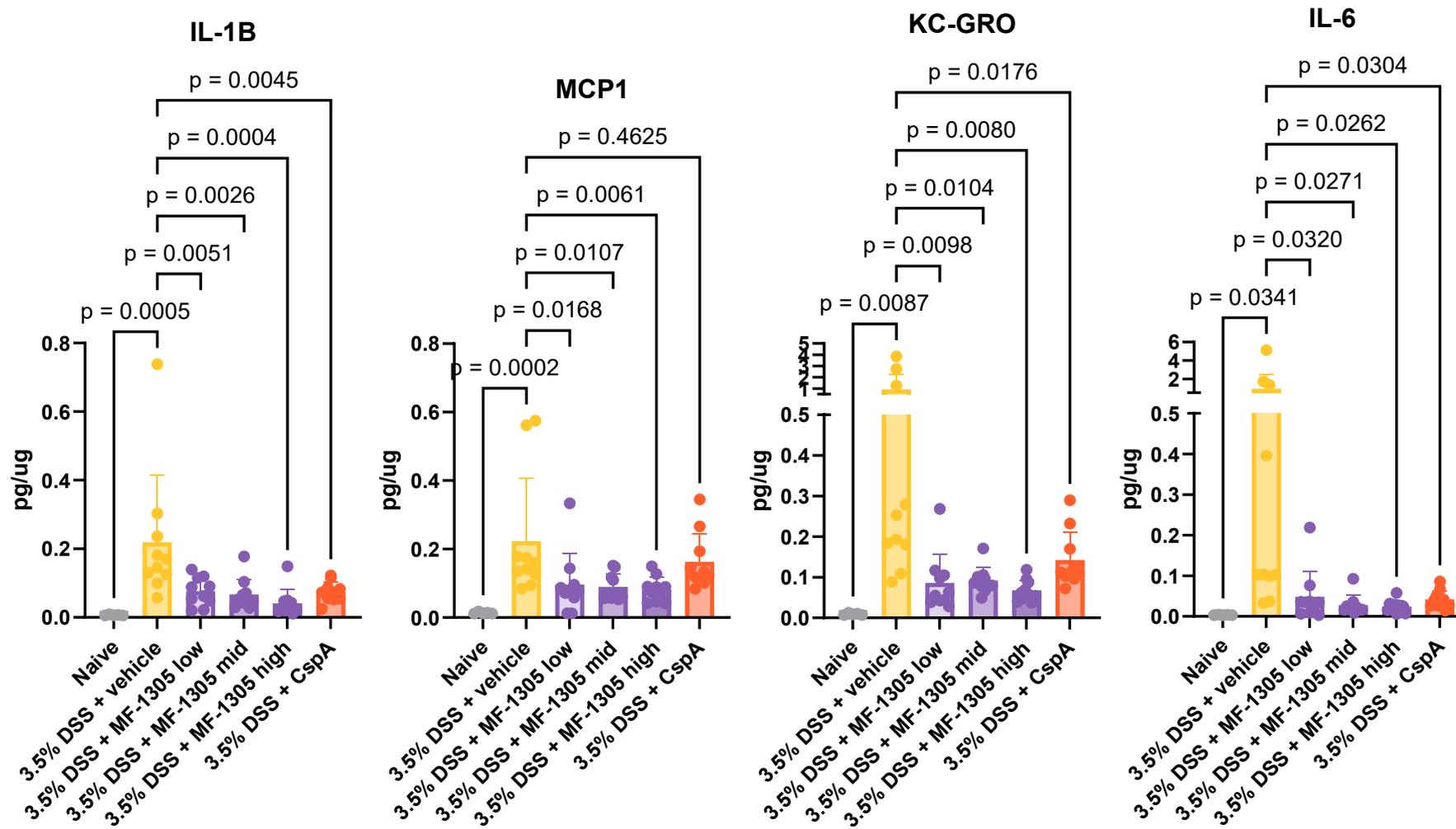
MF-1305 preserved body weight

MF-1305 reduced fecal blood content

MF-1305 improved stool consistency

Two-way ANOVA; Dunnett's test for multiple comparisons
 * $p \leq .0239$, *** $p \leq .0004$, **** $p < .0001$ for all MF-1305 doses compared to DSS + veh

MF-1305 Significantly Reduced Colon Cytokines

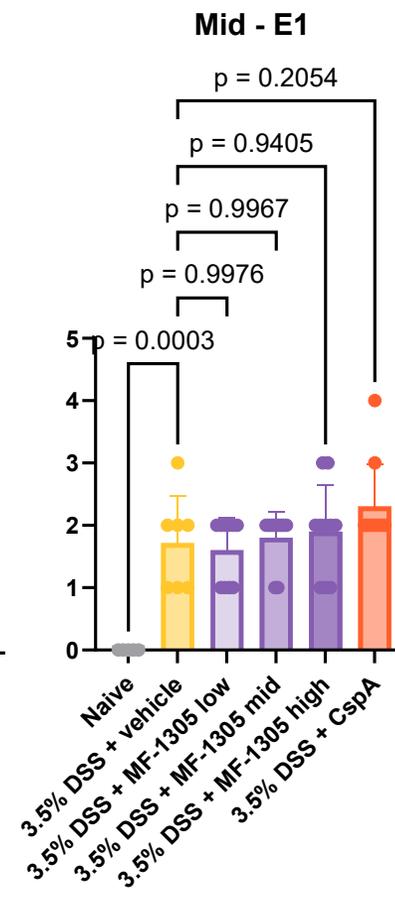
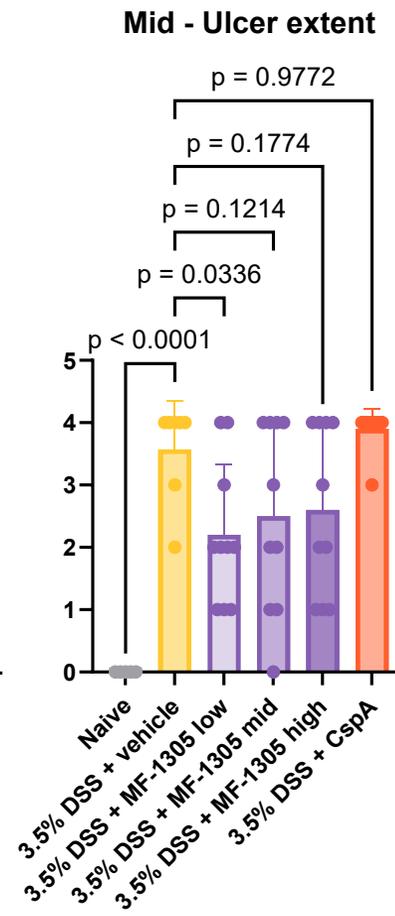
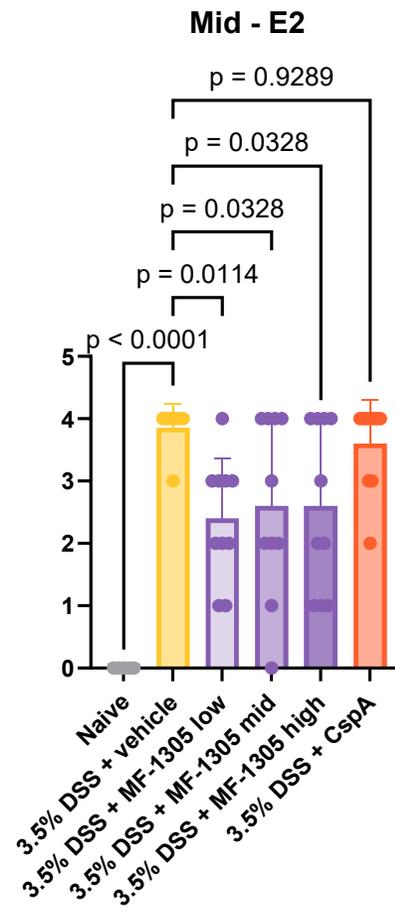
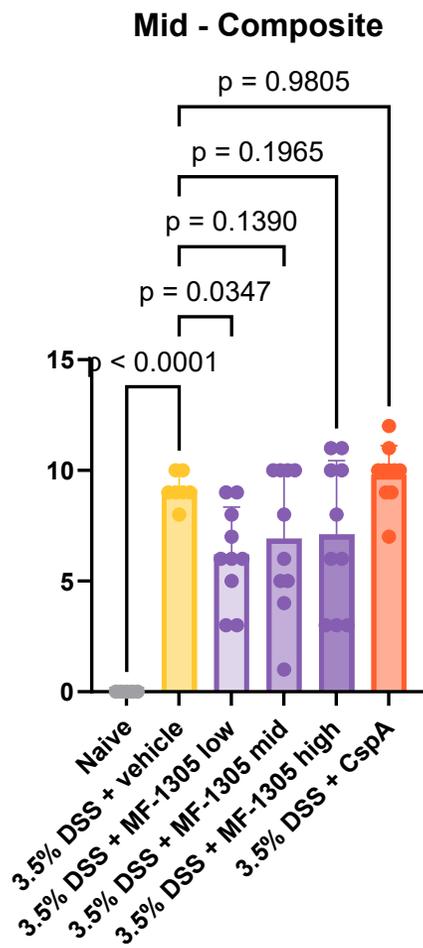


Two-way ANOVA, Dunnett's multiple comparisons test
 N = 3 DSS Veh group samples collected on Day 10 excluded from graphs
 TNF- α – high rate of BQL results, not included here

Benefits observed on tissue architecture (i.e., E2) and ulcer extent

Overall Ulcer Extent Score:	
0	normal
1	<10%
2	10-19%
3	20-29%
4	>30%
E1: % of section affected by any inflammatory changes	
0	normal
1	1 - 25%
2	26 - 50%
3	51 - 75%
4	76 - 100%
E2: % of section affected by severe inflammatory changes with obliteration of normal architecture, erosion/ulceration and/or crypts abscesses	
0	normal
1	<10%
2	10-19%
3	20-29%
4	>30%

Adapted from Burich, 2001 and Hausmann, 2007



Mid-Section: Positive Detailed Histological Data Available under CDA

Two-way ANOVA, Dunnett's multiple comparisons test
 N = 3 DSS Veh group samples collected on Day 10 excluded from graphs

- MF-1305 significantly improved Disease Activity Index (DAI): body weight, fecal blood, and stool consistency.
- MF-1305 improved survival
- MF-1305 significantly reduced colon cytokine levels.
- MF-1305 significantly improved histological disease including ulceration and tissue architecture in colon mid-section.

Thank you
www.epirium.com