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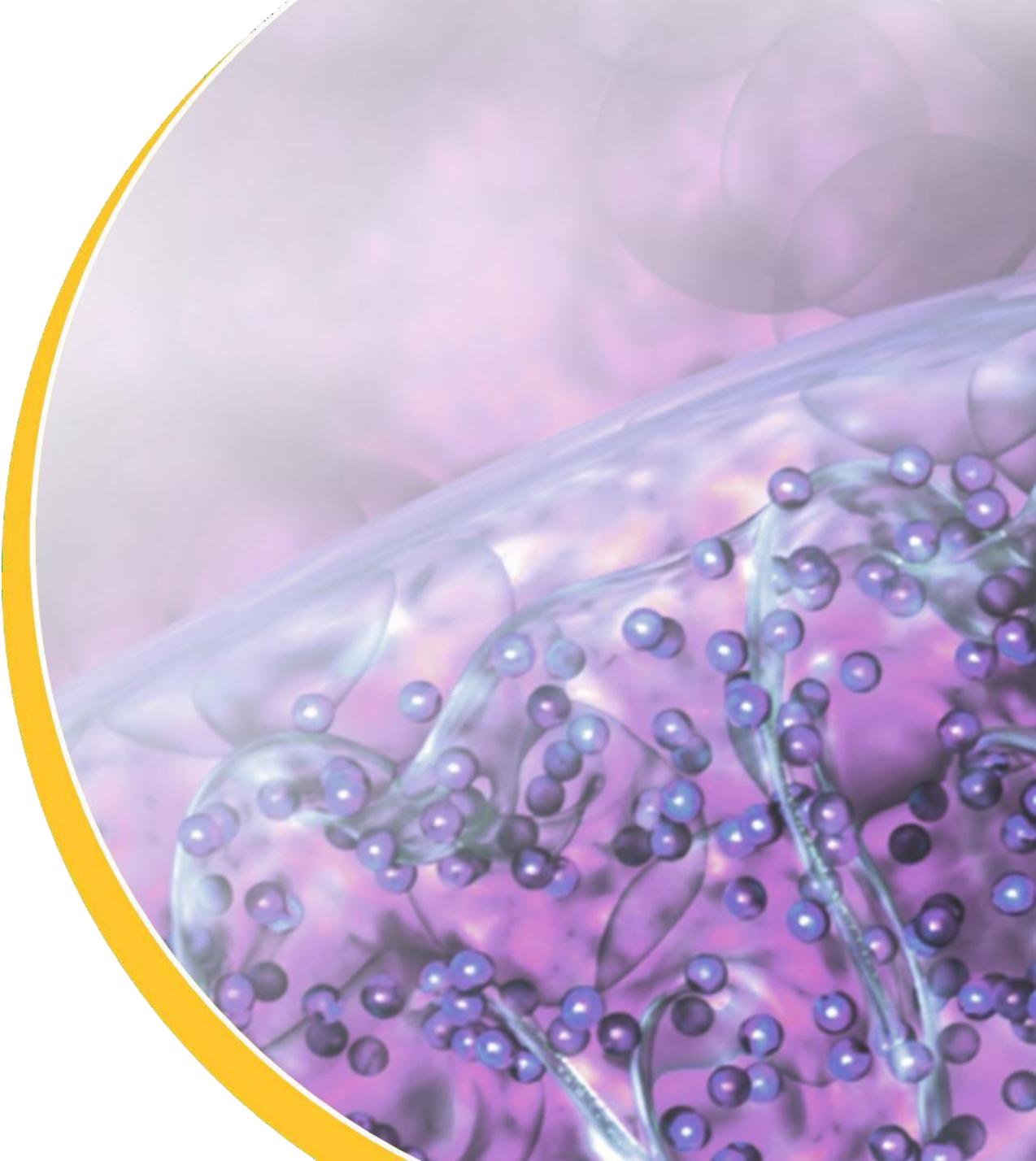
Oral 15-PGDH Inhibitor Platform:
Leveraging PGE2 Signaling To Treat Sarcopenia, Neuromuscular & Inflammatory Diseases (IBD):

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

Experienced Team with a Demonstrated Track Record of Success

Epirium Bio

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 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

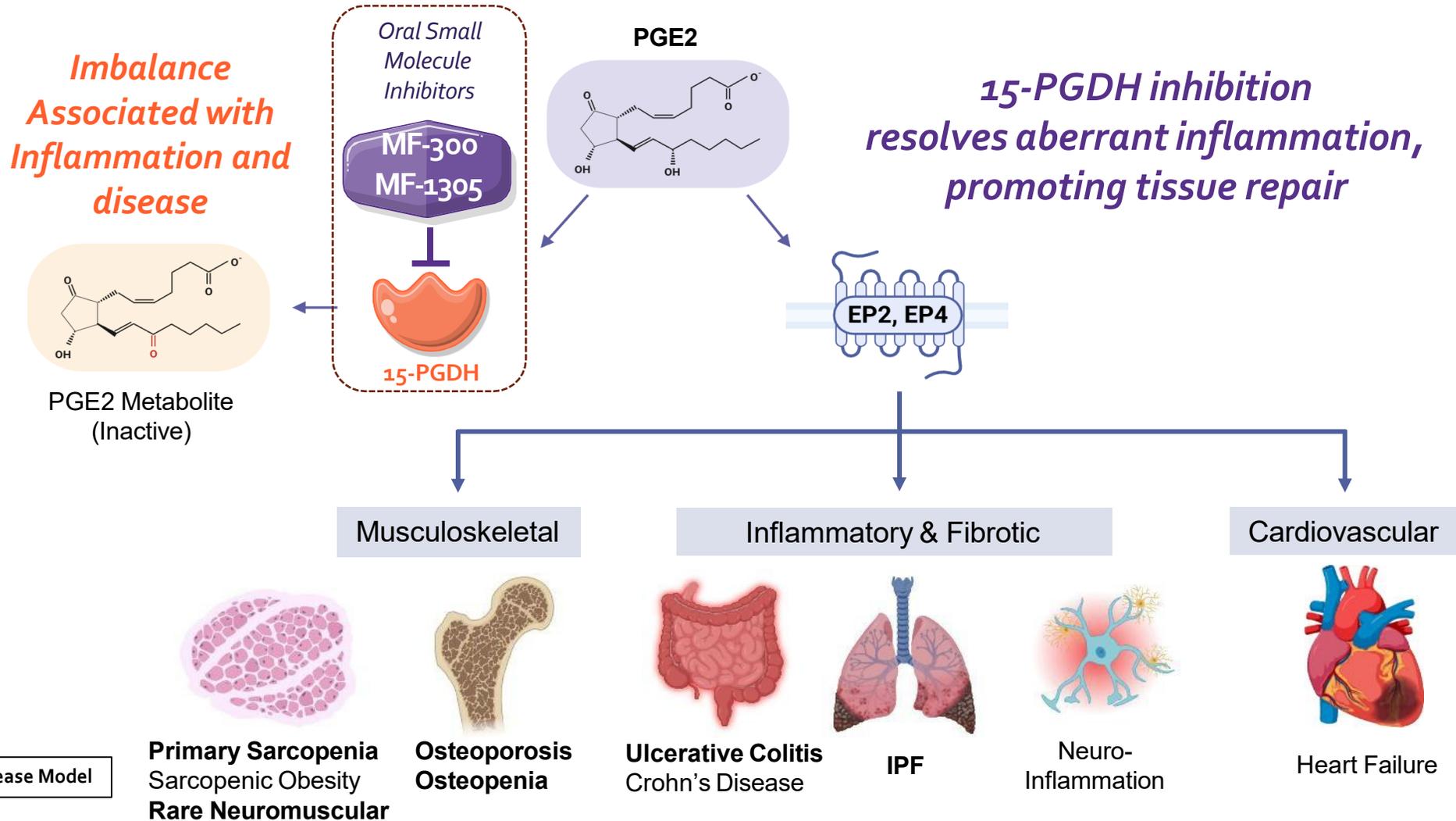Formerly served as CSO and head of regulatory & medical affairs at Gelesis
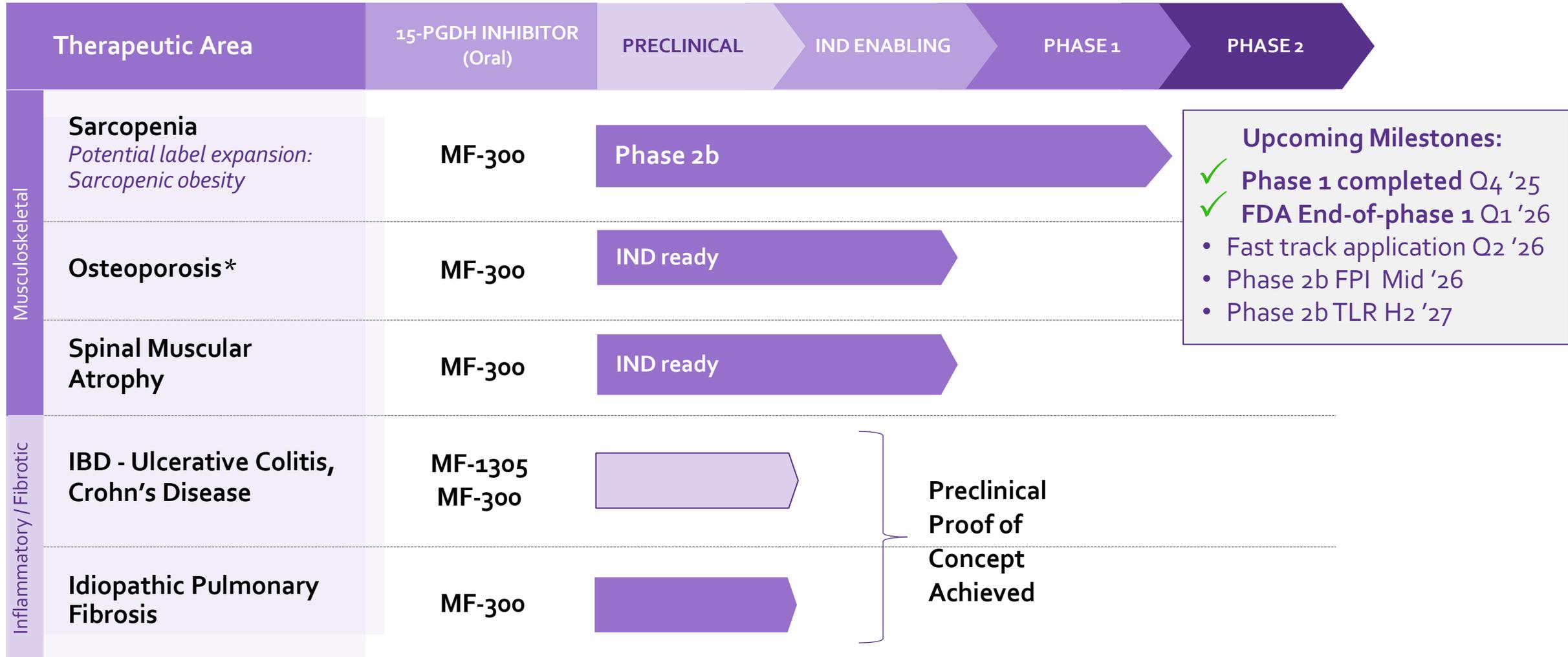
Lois Lee, Pharm.D. Clinical Development

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 signaling in restoring tissue homeostasis: rebalancing inflammation, stimulating regeneration, reducing fibrosis

Imbalance Associated with Inflammation and disease

Oral Small Molecule Inhibitors

MF-300
MF-1305

PGE2

15-PGDH inhibition resolves aberrant inflammation, promoting tissue repair

15-PGDH

PGE2 Metabolite (Inactive)

EP2, EP4

| Musculoskeletal | Inflammatory & Fibrotic | Cardiovascular |

Primary Sarcopenia
Sarcopenic Obesity
Rare Neuromuscular

Osteoporosis
Osteopenia

Ulcerative Colitis
Crohn's Disease

IPF

Neuro-Inflammation

Heart Failure

BOLD = Efficacy in Disease Model

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			
Osteoporosis*	**MF-300**	IND ready			
Spinal Muscular Atrophy	**MF-300**	IND ready			
Inflammatory / Fibrotic					
IBD - Ulcerative Colitis, Crohn's Disease	**MF-1305 MF-300**				
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**
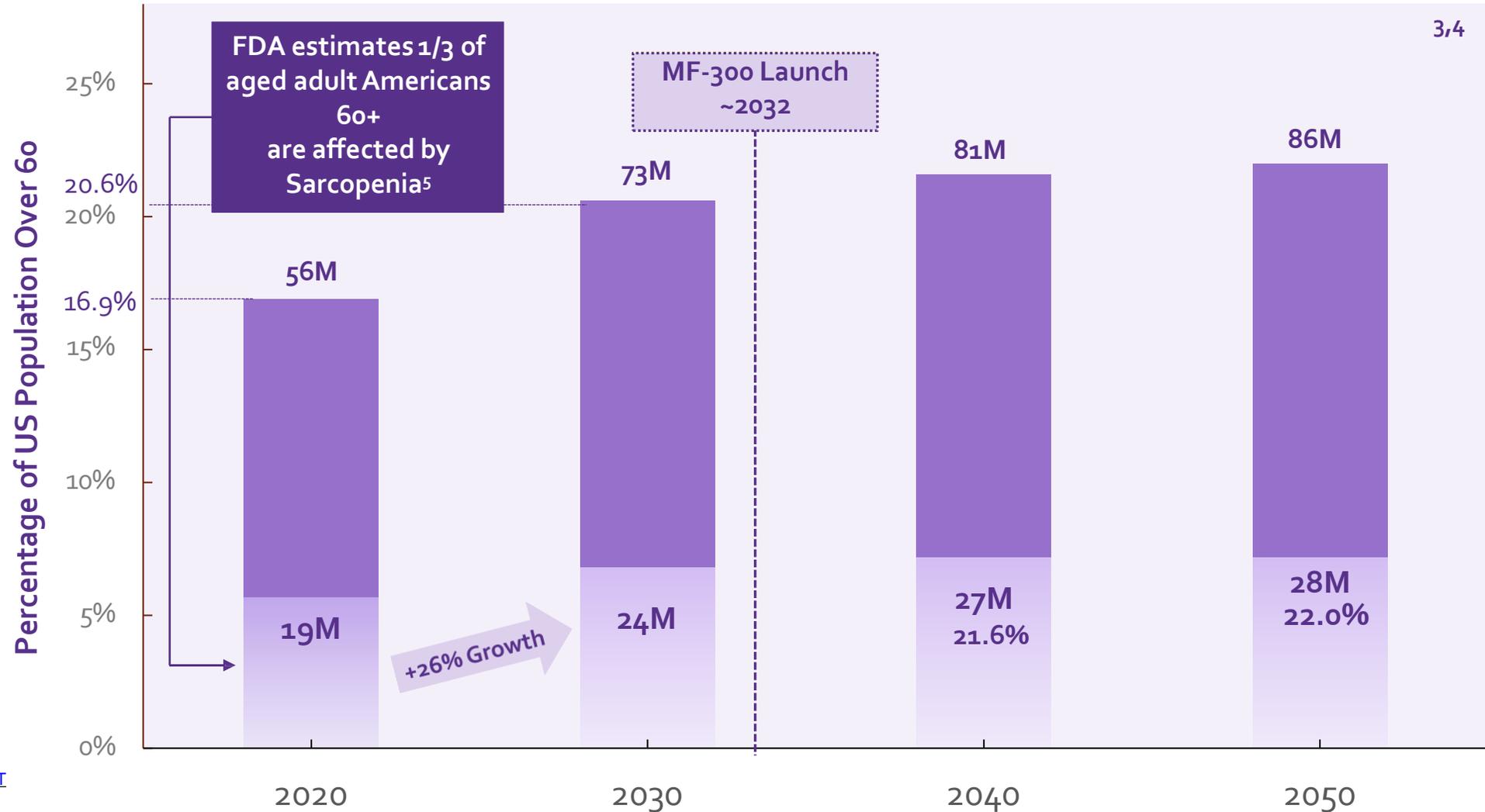
- **Preclinical Muscle Force & Biomarker Results**

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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
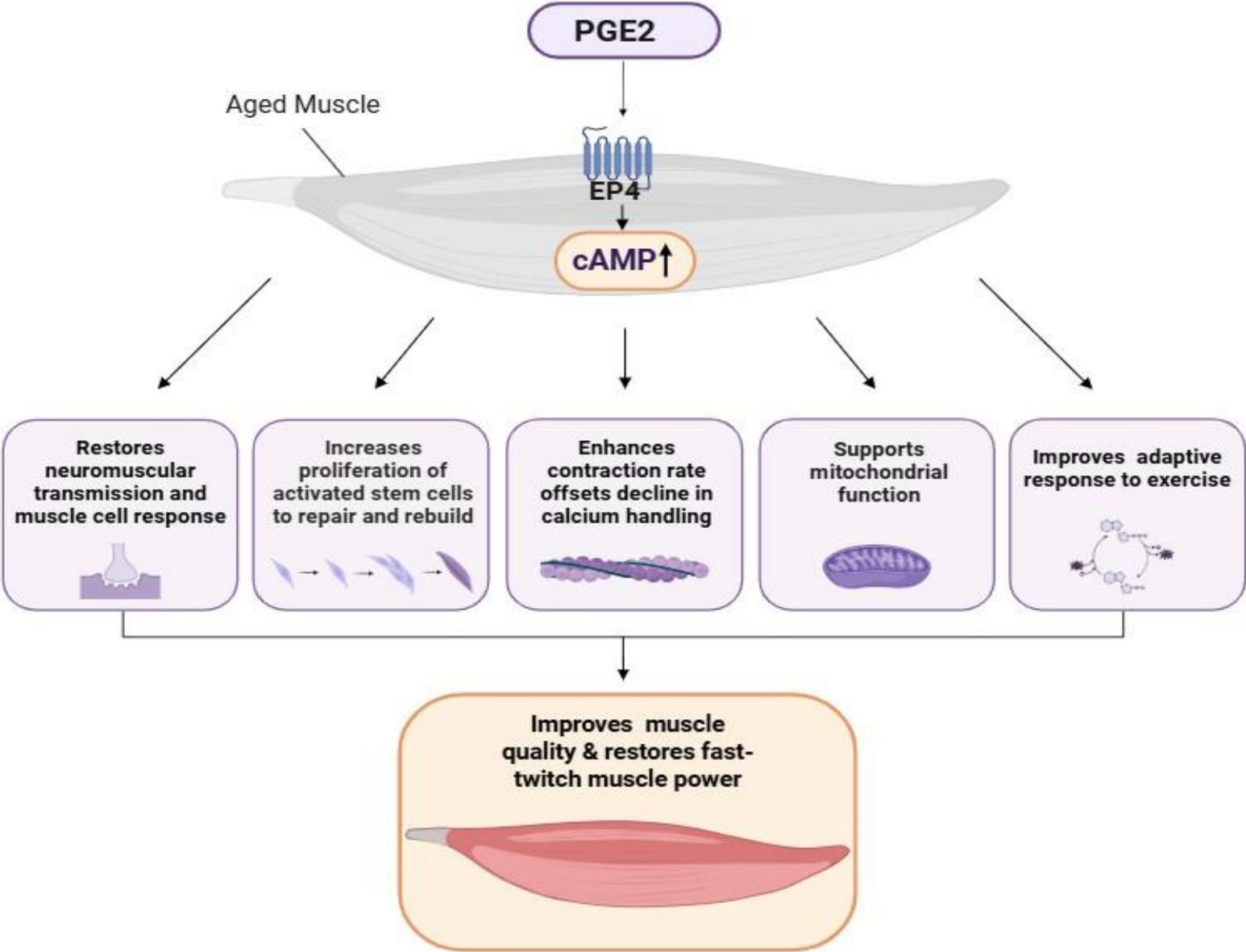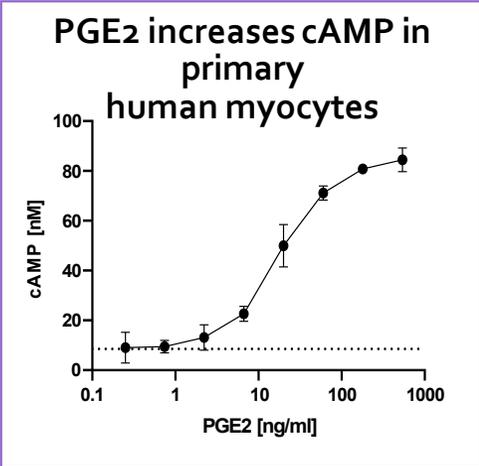Increased Morbidity & Mortality[2]

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.
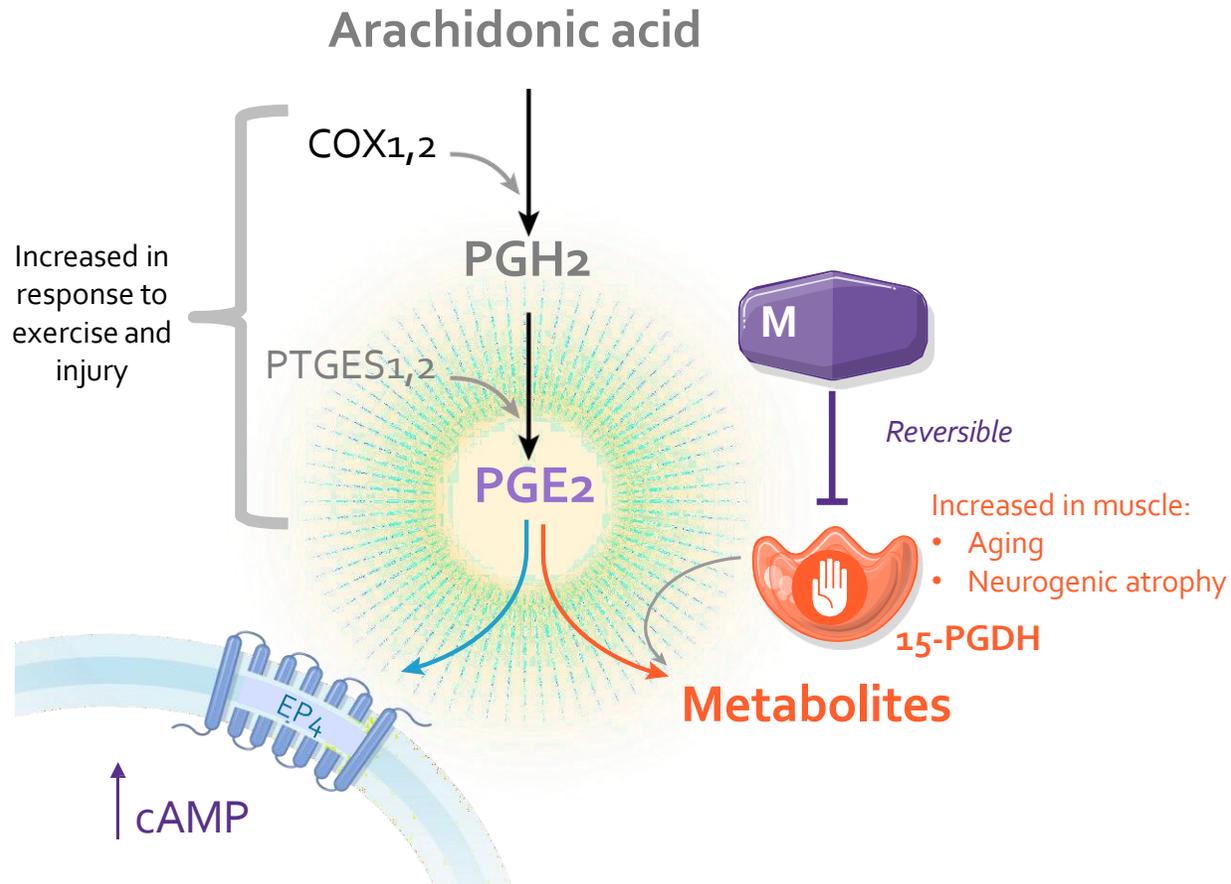5. https://www.fda.gov/files/about%20ofda/published/The-Voice-of-the-Patient--Sarcopenia.pdf

Percentage of US Population Over 60

FDA estimates 1/3 of aged adult Americans 60+ are affected by Sarcopenia[5]

MF-300 Launch ~2032

[3,4]

25%
20.6%
20%
16.9%
15%
10%
5%
0%

- 2020: 56M / 19M
- 2030: 73M / 24M — +26% Growth
- 2040: 81M / 27M / 21.6%
- 2050: 86M / 28M / 22.0%

PGE2 Increases cAMP Resulting in Improved Muscle Quality

PGE2 increases cAMP in primary human myocytes

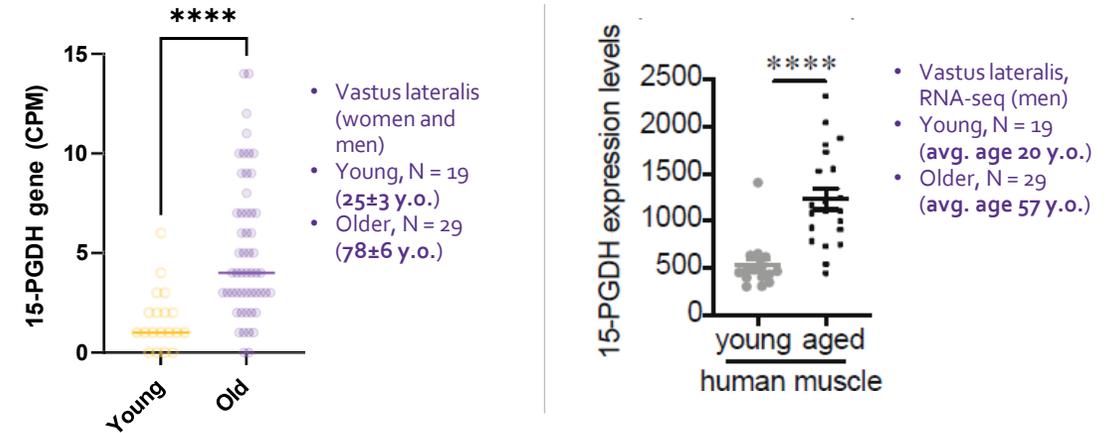Berdeaux et al., 2012
Ho et al., 2017
Palla et al., 2021
Bakooshli et al., 2023
Epirium unpublished data

PGE2

Aged Muscle

EP4

cAMP↑

Restores neuromuscular transmission and muscle cell response

Increases proliferation of activated stem cells to repair and rebuild

Enhances contraction rate offsets decline in calcium handling

Supports mitochondrial function

Improves adaptive response to exercise
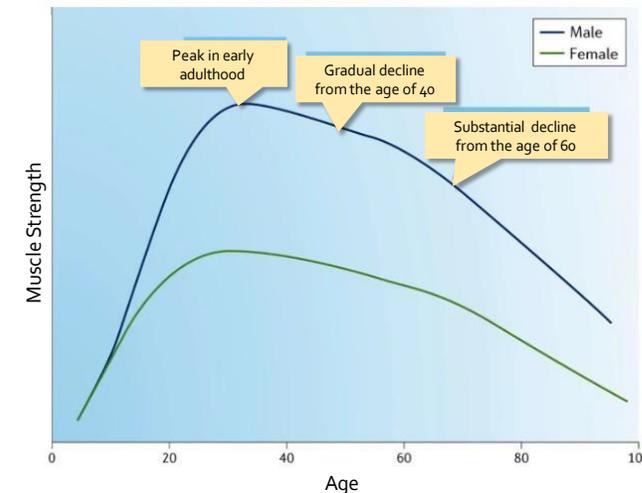
Improves muscle quality & restores fast-twitch muscle power

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

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

Arachidonic acid

COX1,2

Increased in response to exercise and injury

PGH2

PTGES1,2

M

Reversible

PGE2

Increased in muscle:
- Aging
- Neurogenic atrophy

15-PGDH

EP4

Metabolites

↑ cAMP

15-PGDH gene (CPM)

****

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

15-PGDH expression levels

****

- Vastus lateralis, RNA-seq (men)
- Young, N = 19 (avg. age 20 y.o.)
- Older, N = 29 (avg. age 57 y.o.)

young aged
human muscle

Grip strength, a predictor of sarcopenia risk, declines with age[5]

Peak in early adulthood

Gradual decline from the age of 40

Substantial decline from the age of 60

— Male
— Female

Muscle Strength

Age

[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
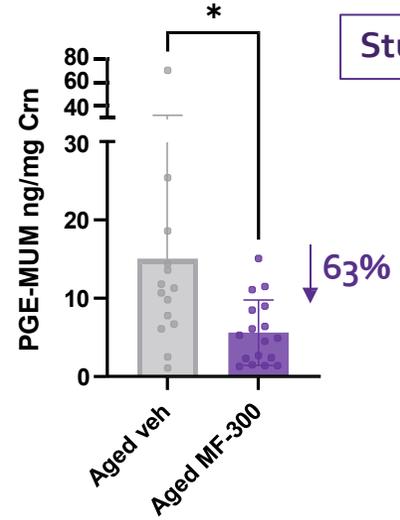
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Preclinical Sarcopenia Studies

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

Study 1

Vehicle
MF-300 target dose mg/kg

↓ 43%

PGE-MUM ↓ ~50% average

Force ↑ ~20% average

Study 2

↓ 63%

23% Increase

Aged veh vs. Aged MF-300 target dose   ***   0.0001

17% Increase

Aged veh vs. Aged MF-300 target dose   ***   0.0006
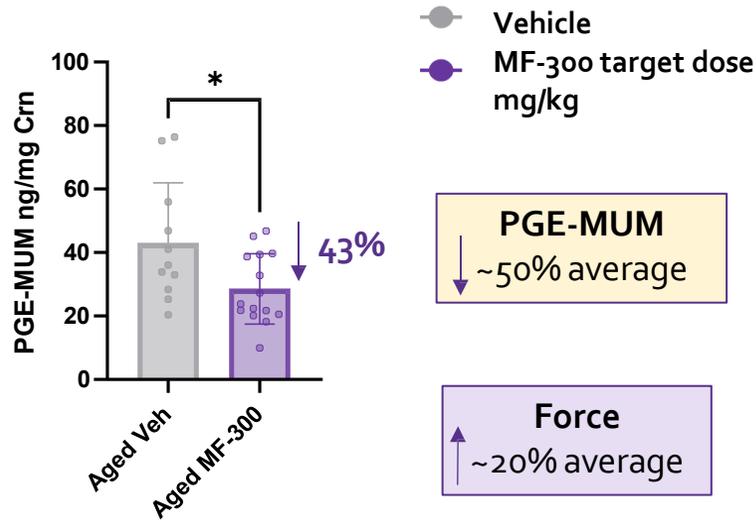
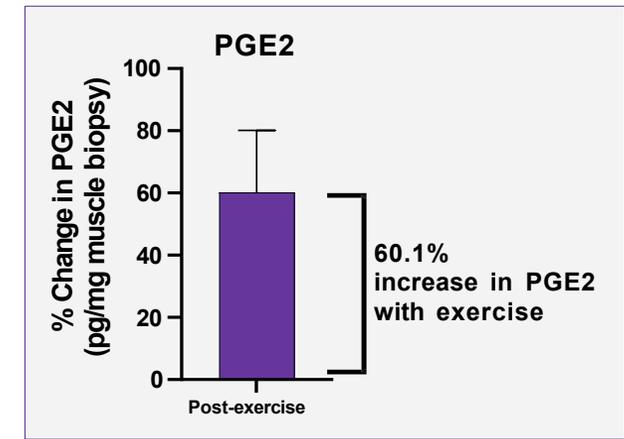## Target Engagement Biomarker

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

PGE2 in human muscle

PGE2

60.1% increase in PGE2 with exercise
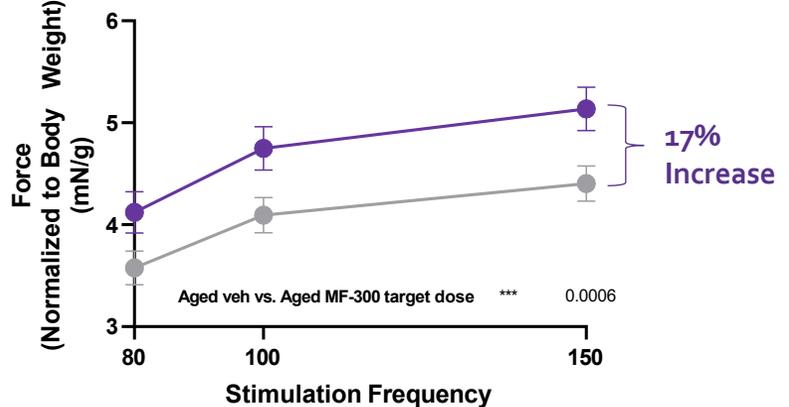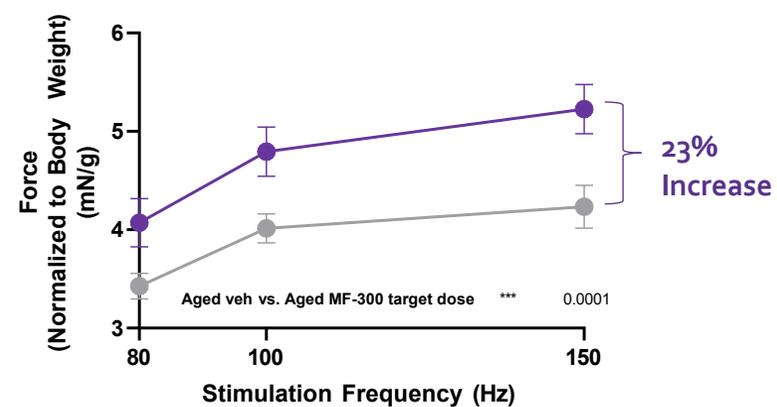
Post-exercise

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

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 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 $\geq 50\%$ reduction in PGE-MUM
- ✓ Evidence of mechanism-increased PGE2 levels
- ✓ Clear dose/response relationship defining therapeutic range, supportive of Phase 2b dose selection

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MF-   '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

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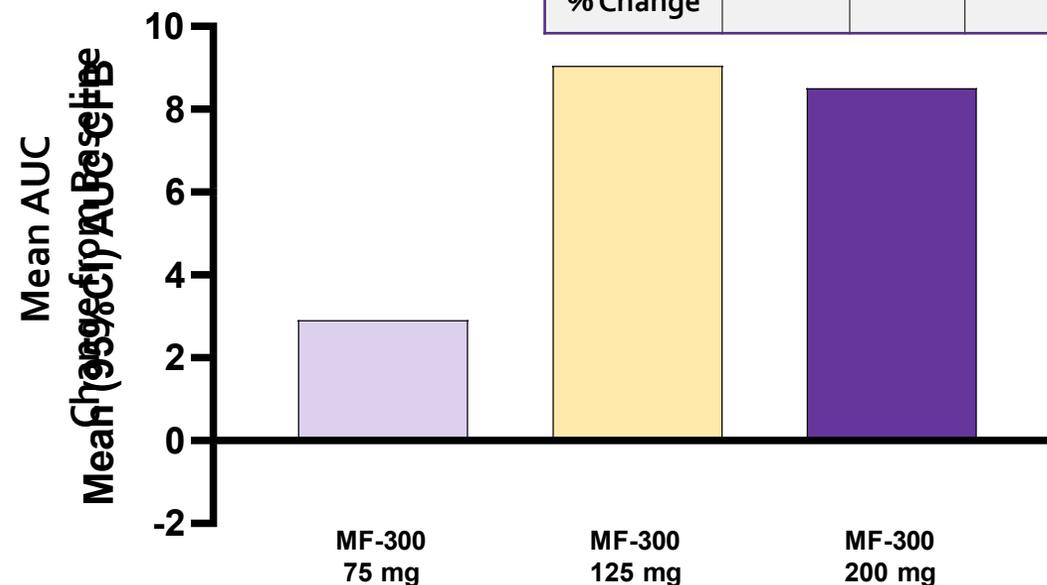
Placebo-adjusted PGE-MUM Change from Baseline (95% CI)

MF-300 (mg)	75	125	200
Placebo Adj. % Change	-64%	-64%	-83%*
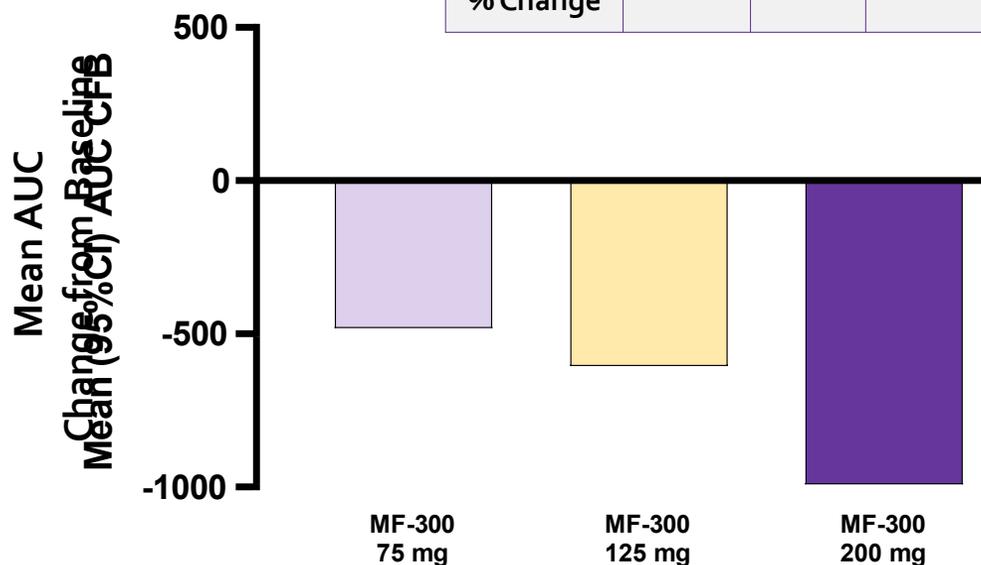
*p<0.05 versus placebo (95% CI does not include 0)

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

% Achieving Goal

- MF-300 75 mg: 4/8 — 50%
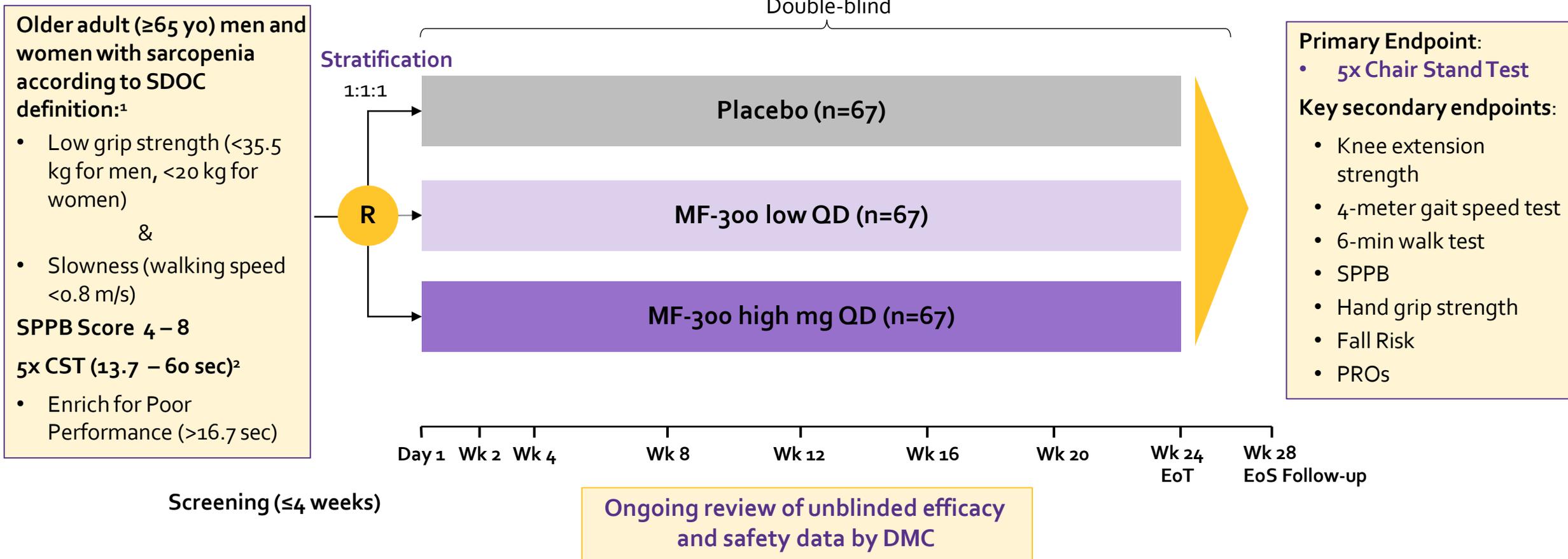- MF-300 125 mg: 5/8 — 63%
- MF-300 200 mg: 6/8 — 75%
- Placebo: 0/6
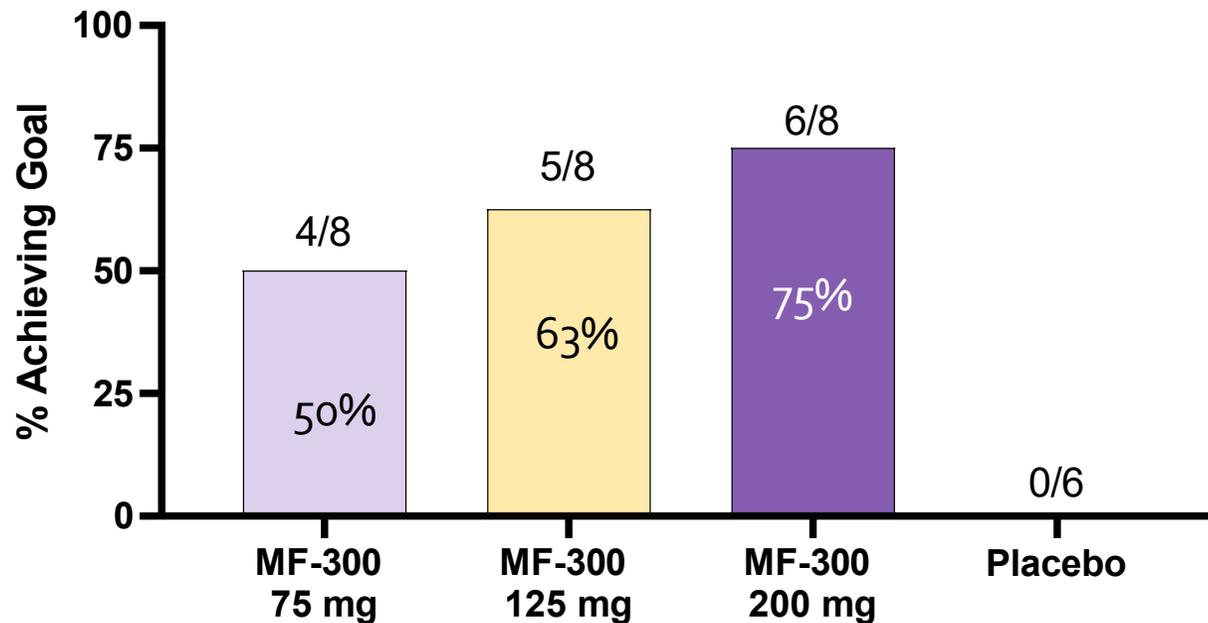
Rationale for targets:

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

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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)

Screening (≤4 weeks)

Double-blind

Stratification

1:1:1

R

Placebo (n=67)

MF-300 low QD (n=67)

MF-300 high mg QD (n=67)

Day 1 Wk 2 Wk 4   Wk 8   Wk 12   Wk 16   Wk 20   Wk 24   Wk 28
                                                                      EoT   EoS Follow-up

Ongoing review of unblinded efficacy and safety data by DMC

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

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

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- **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-   's mechanism of action,** which targets fast-twitch muscle and primarily lower limb strength

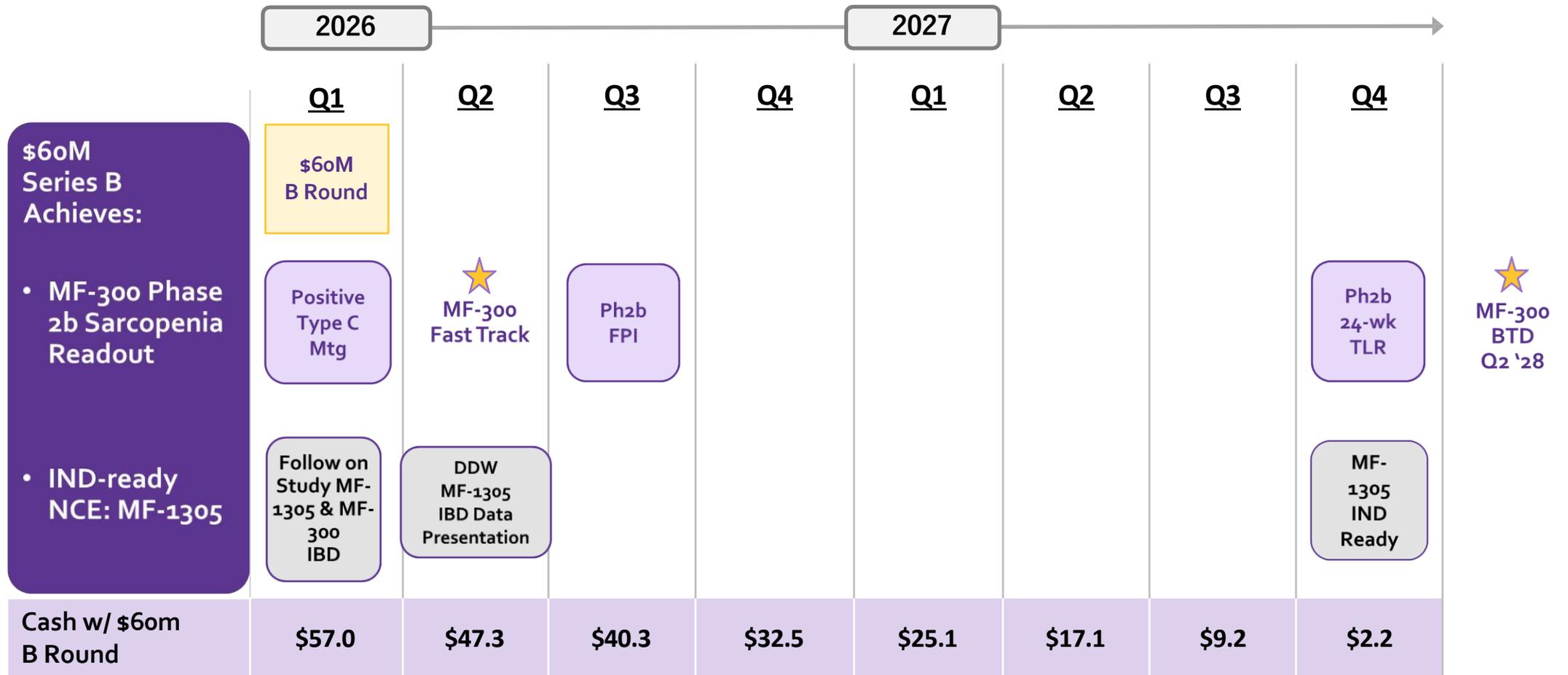- Limited variability and modifiable within 6 months

5xs Chair Stand Test

Start   Repeated 5xs   End
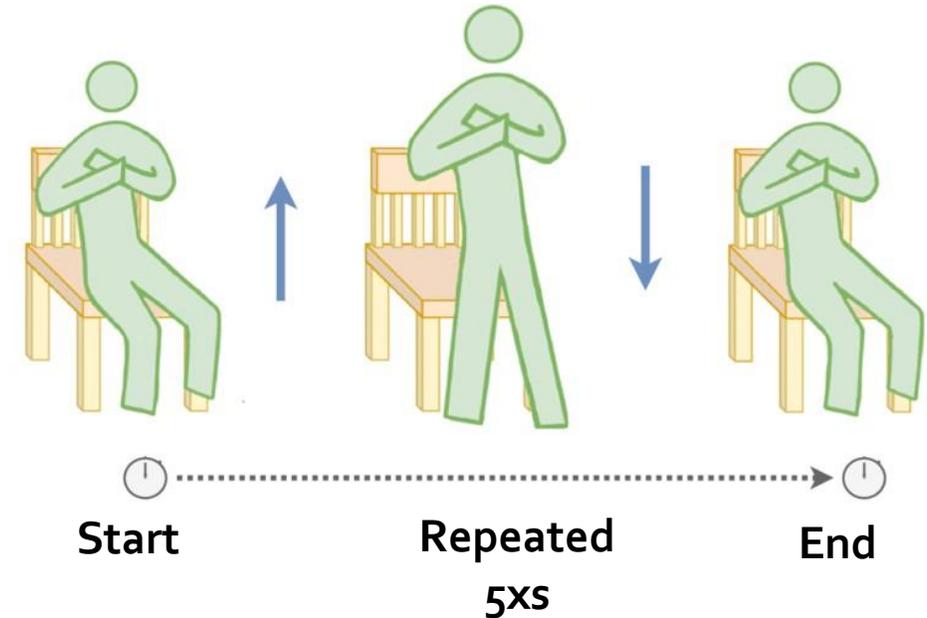
1. ICOPE=Integrated Care for Older People (9789240103726-eng.pdf)

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

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

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	2026				2027			
	Q1	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**	**Q4**
$60M Series B Achieves:	$60M B Round							
• MF-300 Phase 2b Sarcopenia Readout	Positive Type C Mtg	⭐ MF-300 Fast Track	Ph2b FPI					Ph2b 24-wk TLR
• IND-ready NCE: MF-1305	Follow on Study MF-1305 & MF-300 IBD	DDW MF-1305 IBD Data Presentation						MF-1305 IND Ready
Cash w/ $60m B Round	$57.0	$47.3	$40.3	$32.5	$25.1	$17.1	$9.2	$2.2

⭐ MF-300 BTD Q2 '28

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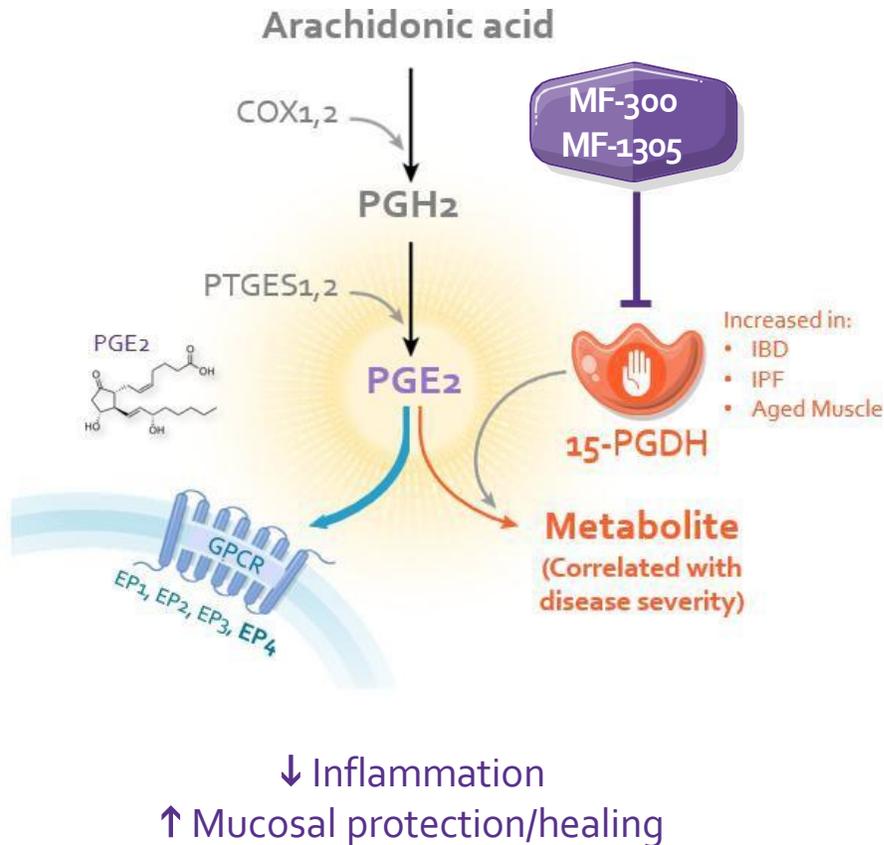
Positive IBD Results:

MF-1305 DSS Mouse IBD Colitis Study

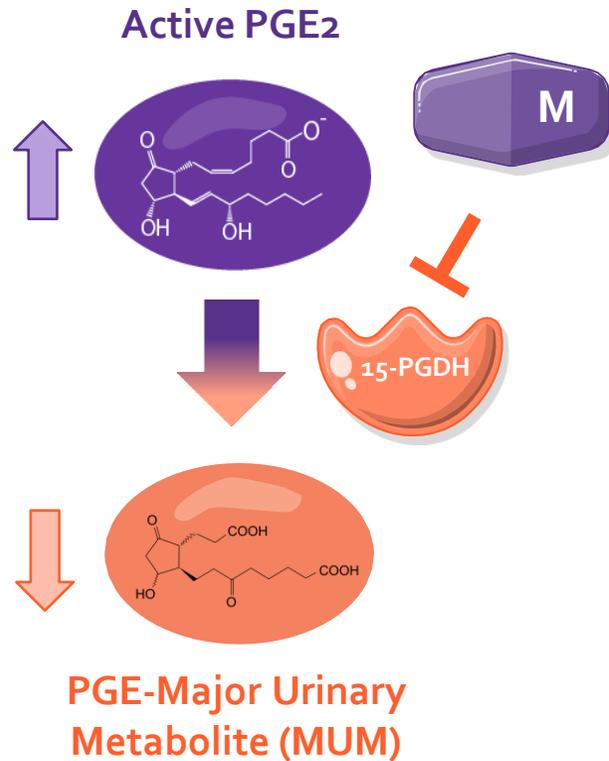- Supportive Scientific Rationale

- Detailed Treatment Study Results

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

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The PGE2/EP4 axis improves outcomes in DSS colitis models

Arachidonic acid

COX1,2

MF-300
MF-1305

PGH2

PTGES1,2

PGE2

Increased in:
• IBD
• IPF
• Aged Muscle

15-PGDH

GPCR

EP1, EP2, EP3, EP4

Metabolite
(Correlated with disease severity)

↓ Inflammation
↑ Mucosal protection/healing

Intervention / genetic model	Species & colitis model	Key outcomes	Reference
SW033291 (15-PGDH inhibitor, IP)	Mouse, DSS colitis	• 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	• Improved DAI • Improved colon length • Improved histological measures	Li et al., 2025
Hpgd knockout (15-PGDH gene)	Mouse, DSS colitis including older mice	• Minimize weight loss • Improved colon length & histology scores	Zhang et al., 2015; Ho et al., 2022
AGN205203 (EP4 agonist)	Mouse, DSS (and DSS+indomethacin) colitis	• Improved DAI • Improved histology: preserved epithelium, reduced epithelial apoptosis, preserved goblet cells, enhanced epithelial regeneration	Jiang et al., 2007
ONO-AE1-329 (EP4 agonist)	Rat & Mouse DSS colitis	• 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 (EP4 agonist)	Mouse, DSS colitis	• Suppressed DSS colitis onset • Promoted histological mucosal healing • Reduced TNFα production • *EP4 antagonist increased mortality*	Watanabe et al., 2015
PGE2 (Exogenous)	Mouse, DSS colitis	• Alleviated mucosal injury • Promoted epithelial protection/healing	Peng et al. 2017

PGE-MUM Links PGE2 & 15-PGDH Activity to Severity of Disease in IBD

Elevated PGE-MUM correlates with active ulcerative colitis in humans

Active PGE2

M

15-PGDH

PGE-Major Urinary Metabolite (MUM)

- **PGE-MUM** is a stable downstream metabolite of PGE2
- **Target engagement & disease biomarker hypothesis for IBD**:
  Reduced PGE-MUM will demonstrate inhibition of 15-PGDH and stabilization of therapeutic PGE2 levels in the diseased intestine

PGE-MUM as a disease response biomarker in IBD

- ✓ Stable PGE$_2$ metabolite[1,2]

- ✓ Elevated in active UC; tracks activity[3,4,5]

- ✓ Detects mucosal healing during clinical remission[6]

- ✓ Reflects CD endoscopic activity[7]

- ✓ Predicts relapse in long duration UC[8]

- ✓ Combination with fecal calprotectin may improve inflammation profiling in UC and CD[9]

[1] Miyamoto et al., 2024
[2] Gross et al., 2005
[3] Arai et al., 2014
[4] Arai et al., 2016
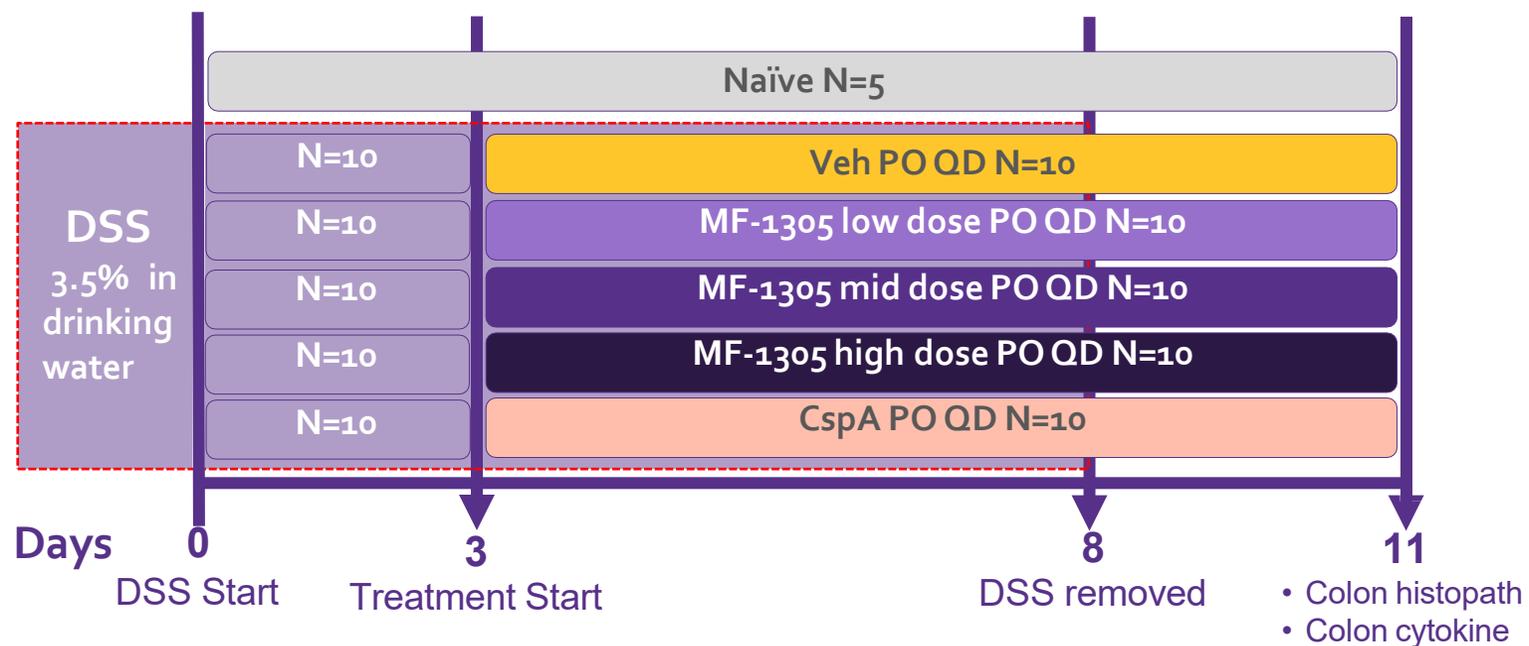[5] Fujiwara et al., 2000
[6] Sakurai et al., 2022
[7] Ishida et al., 2025
[8] Ishida et al., 2022
[9] D'Inca et al., 2025

Oral 15-PGDH Inhibitor MF-1305 DSS Colitis Treatment Study

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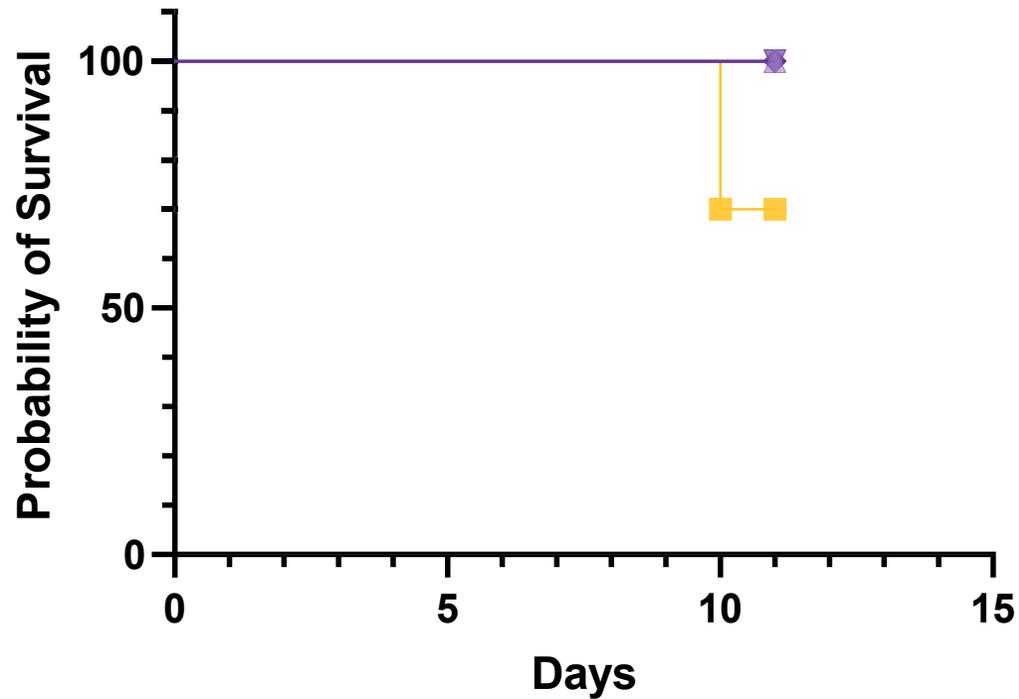- Mouse strain: C57Bl/6
- Sex/Age: Female/10-12 weeks

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

Endpoints:
- Colon
  - Cytokines
  - Histology

Naïve N=5

DSS 3.5% in drinking water

N=10	Veh PO QD N=10
N=10	MF-1305 low dose PO QD N=10
N=10	MF-1305 mid dose PO QD N=10
N=10	MF-1305 high dose PO QD N=10
N=10	CspA PO QD N=10

Days 0 3 8 11

DSS Start   Treatment Start   DSS removed
- Colon histopath
- Colon cytokine

Survival proportions: Survival of DSS

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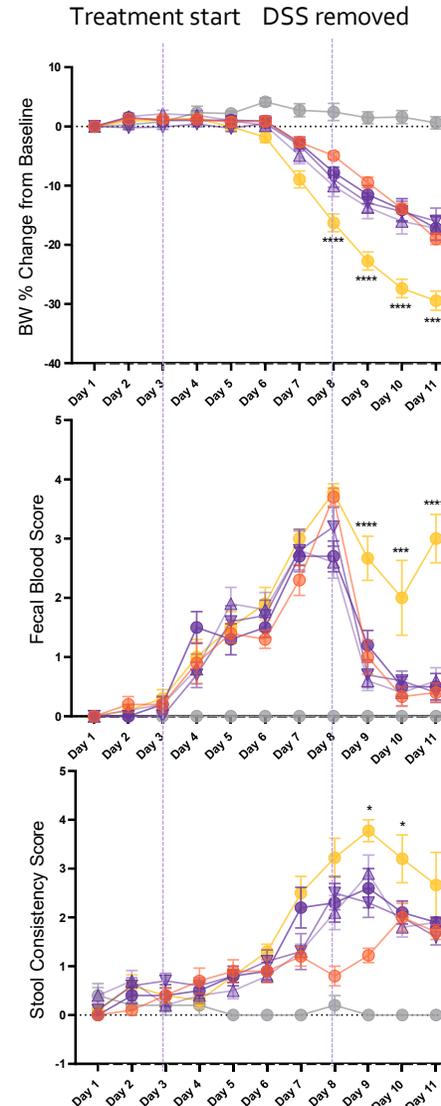
MF-1305 Significantly Improved Disease Activity Index (DAI) & Survival

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**

Legend:
- 3.5% DSS + CspA
- 3.5% DSS + MF-1305 high
- 3.5% DSS + MF-1305 mid
- 3.5% DSS + MF-1305 low
- 3.5% DSS + vehicle
- Naive

Two-way ANOVA; Dunnett's test for multiple comparisons
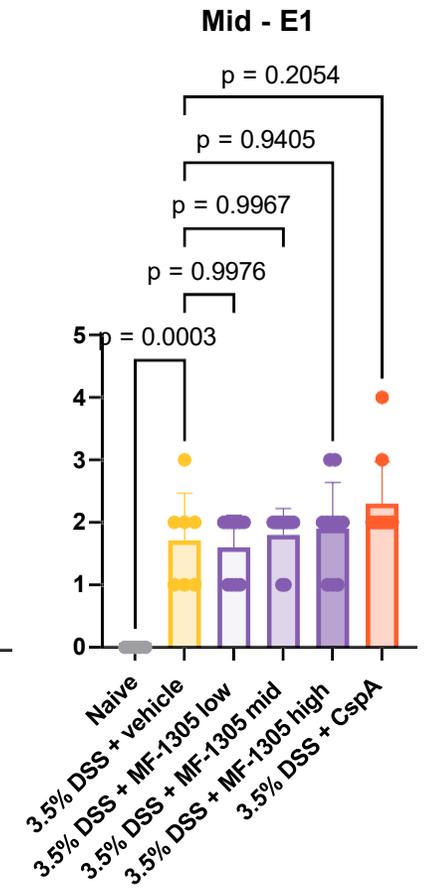*p≤.0239, ***p≤.0004, ****p<.0001 for all MF-1305 doses compared to DSS + veh
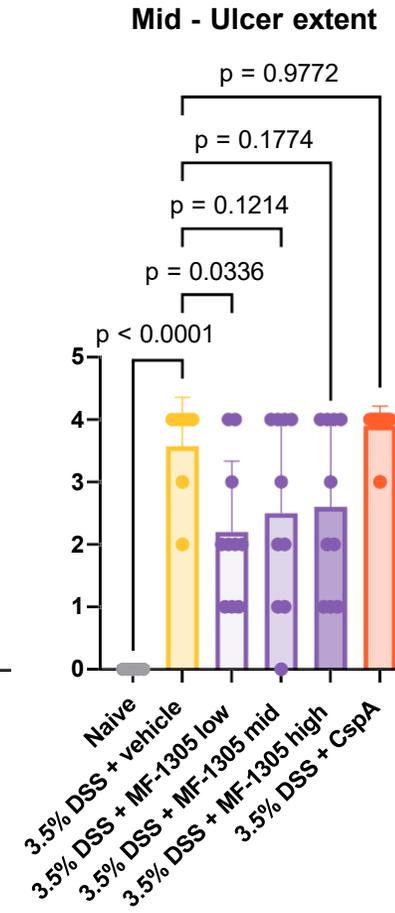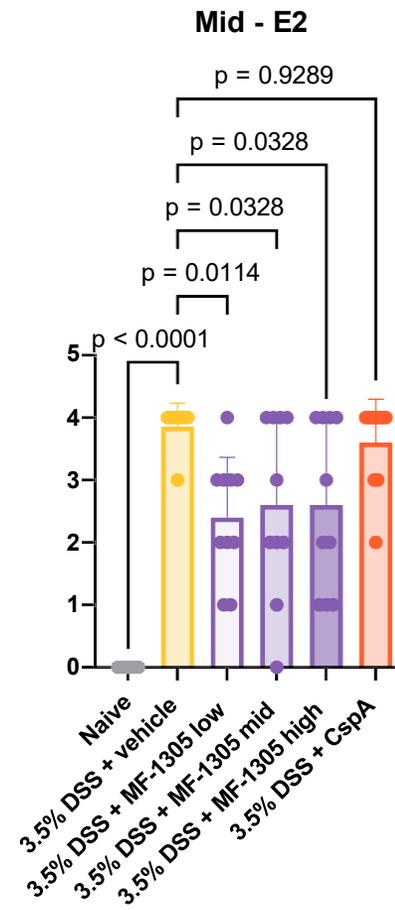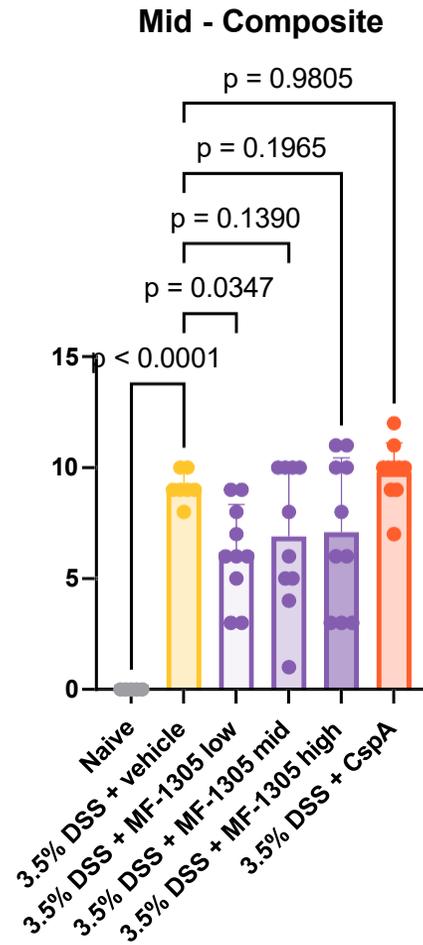
MF-1305 Significantly Reduced Colon Cytokines

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

MF-1305 Significantly Improved Histological Disease in Mid-Colon

Epirium Bio

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 - Composite
p = 0.9805
p = 0.1965
p = 0.1390
p = 0.0347
p < 0.0001

Groups: Naive, 3.5% DSS + vehicle, 3.5% DSS + MF-1305 low, 3.5% DSS + MF-1305 mid, 3.5% DSS + MF-1305 high, 3.5% DSS + CspA

Mid - E2
p = 0.9289
p = 0.0328
p = 0.0328
p = 0.0114
p < 0.0001

Groups: Naive, 3.5% DSS + vehicle, 3.5% DSS + MF-1305 low, 3.5% DSS + MF-1305 mid, 3.5% DSS + MF-1305 high, 3.5% DSS + CspA

Mid - Ulcer extent
p = 0.9772
p = 0.1774
p = 0.1214
p = 0.0336
p < 0.0001

Groups: Naive, 3.5% DSS + vehicle, 3.5% DSS + MF-1305 low, 3.5% DSS + MF-1305 mid, 3.5% DSS + MF-1305 high, 3.5% DSS + CspA

Mid - E1
p = 0.2054
p = 0.9405
p = 0.9967
p = 0.9976
p = 0.0003

Groups: Naive, 3.5% DSS + vehicle, 3.5% DSS + MF-1305 low, 3.5% DSS + MF-1305 mid, 3.5% DSS + MF-1305 high, 3.5% DSS + CspA

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

Epirium Bio

- 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
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