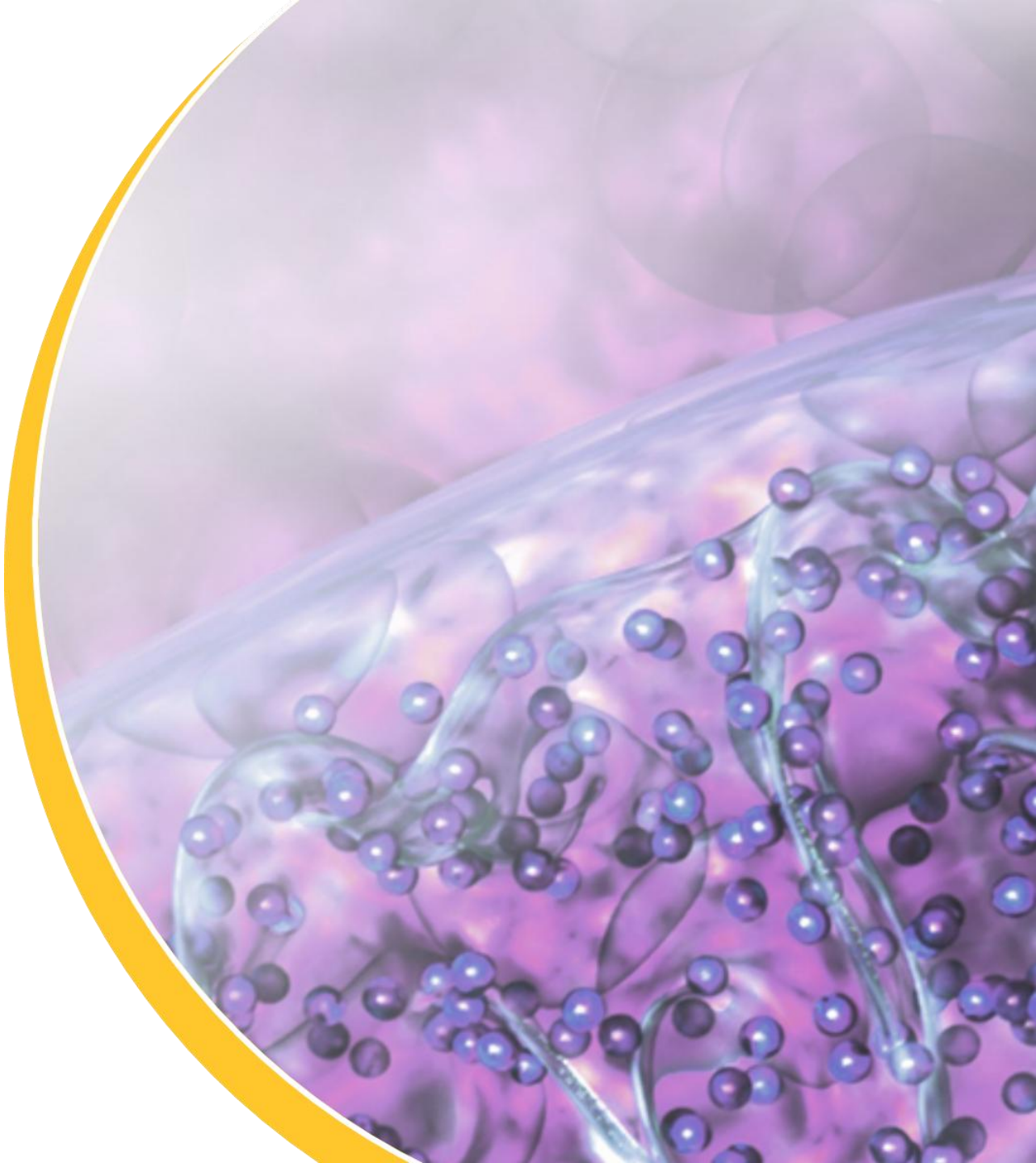
Epirium Bio

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 (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 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

Roger Fielding, Ph.D. Professor of Medicine

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

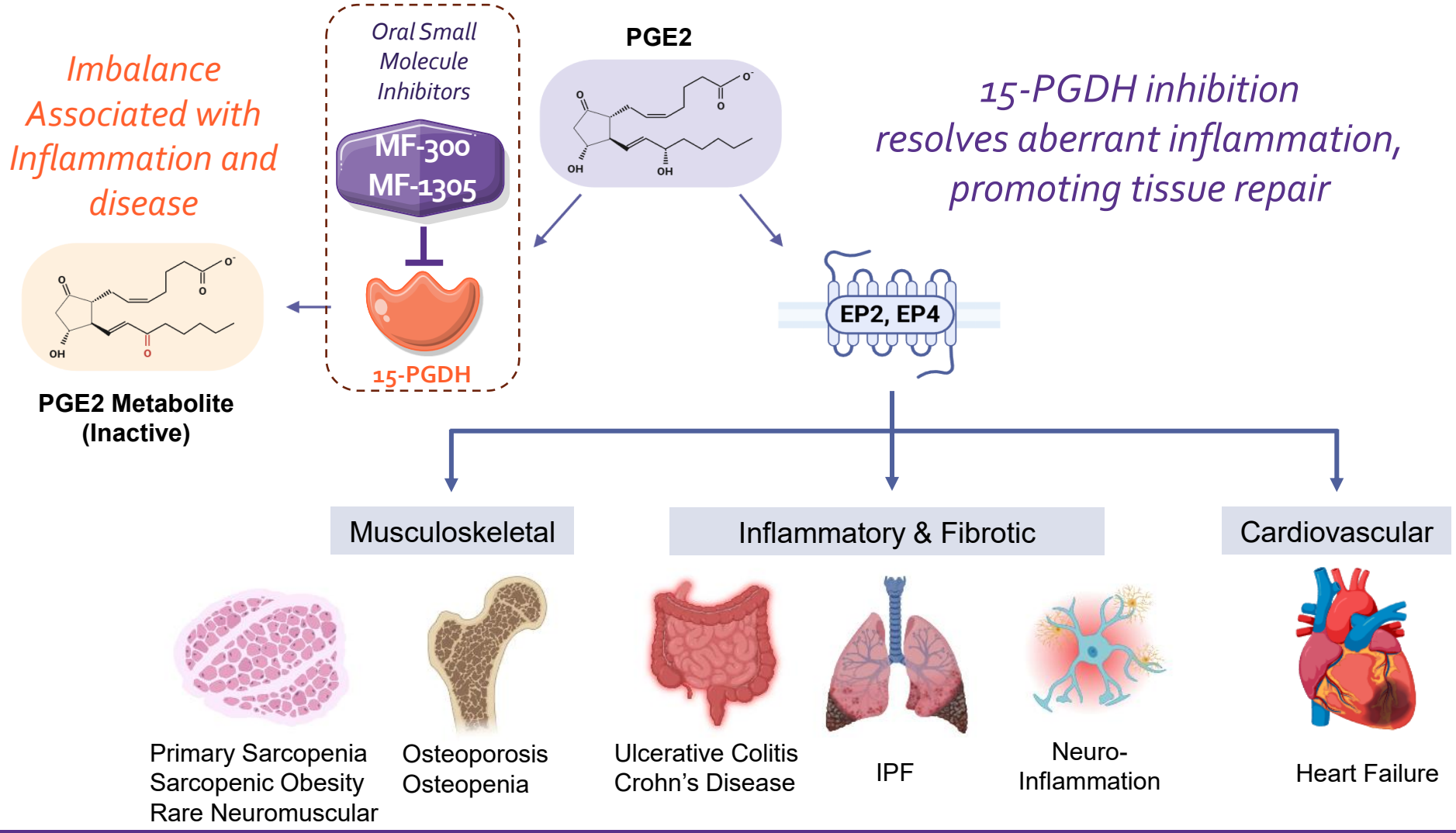
Published over 200 per-reviewed papers and 8,000 citations

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

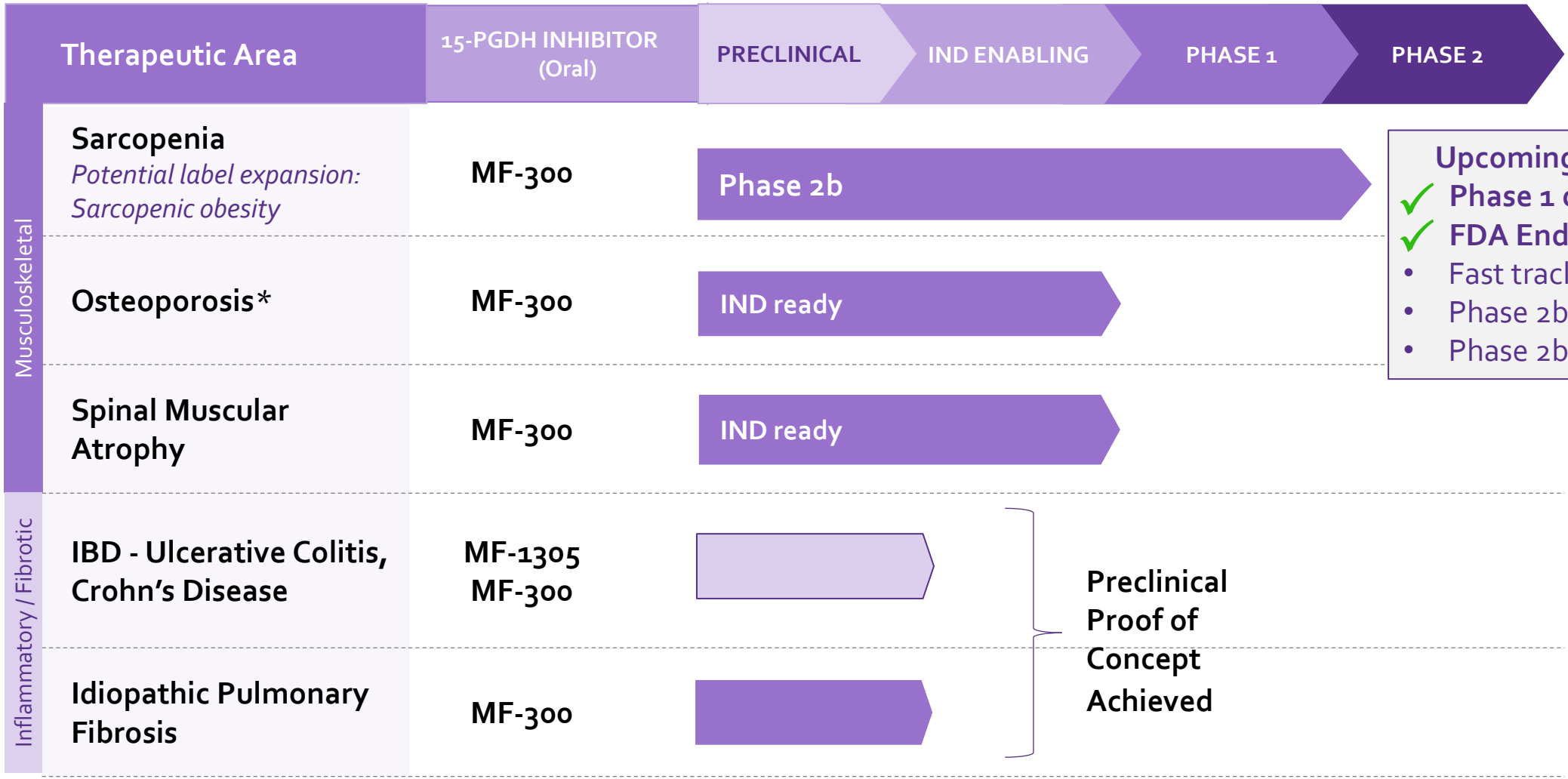
Pipeline in a Mechanism: Unifying Biology Addressing Blockbuster Markets

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"



*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

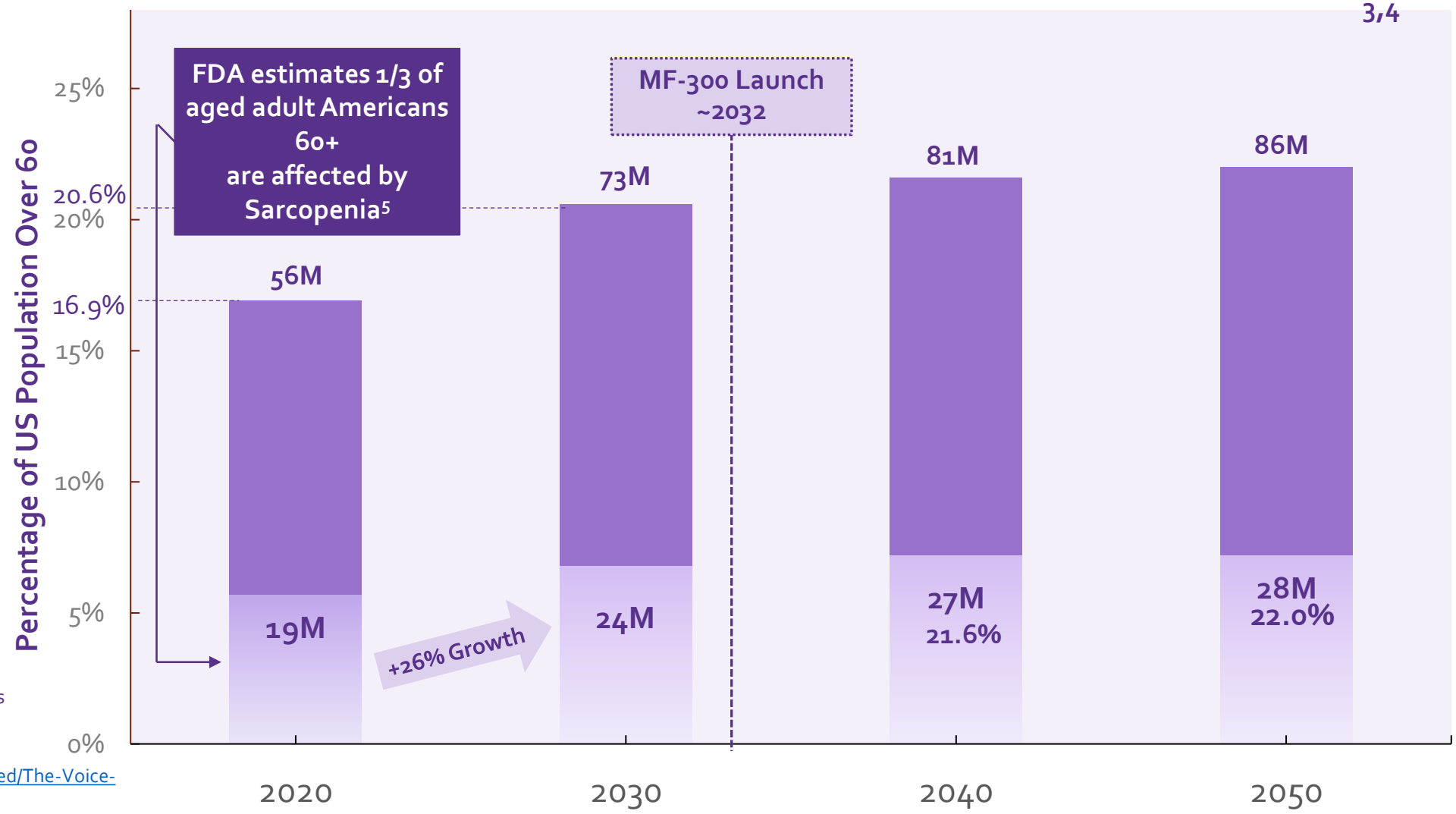
Sarcopenia: Large and Growing Unmet Medical Need w/ No FDA Approved Therapy

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 in Human Muscle Cells & Improves Muscle Function in Aged Mice

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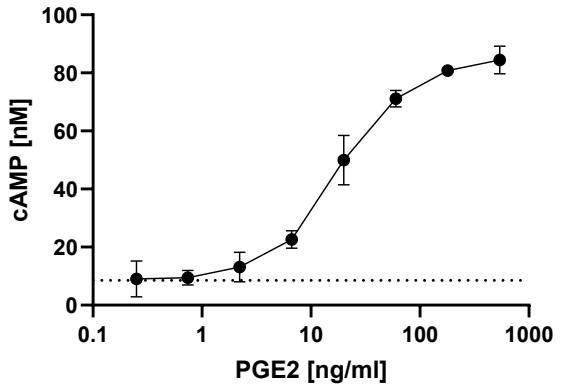
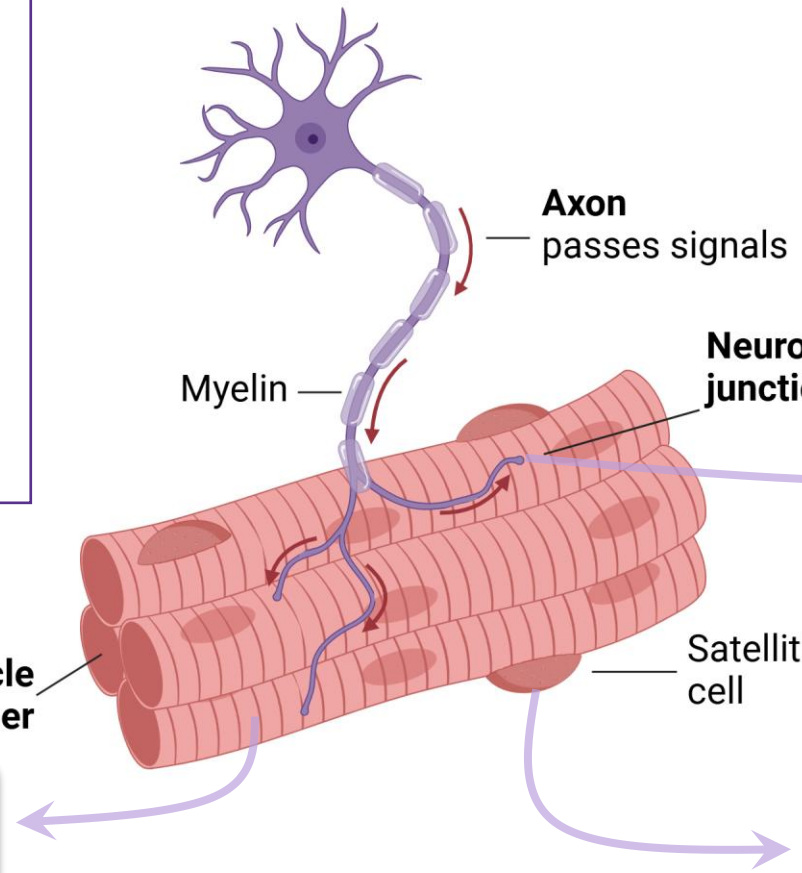
PGE2 increases cAMP in primary human myocytes



Epirium cell-based assay

15-PGDH ⊥ PGE2 → EP4 → cAMP



NMJ Integrity

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

MUSCLE PHYSIOLOGY

Regeneration of neuromuscular synapses after acute and chronic denervation by inhibiting the gerozyme 15-prostaglandin dehydrogenase

Mohsen A. Bakooshli[1†], Yu Xin Wang[1,2†*], Elena Monti[1], Shiqi Su[1], Peggy Kraft[1], Minas Nalbandian[1], Ludmila Alexandrova[3], Joshua R. Wheeler[4,5], Hannes Vogel[4,5], Helen M. Blau[1*]

Muscle Intrinsic Effects

RESEARCH ARTICLE

Science

AGING

Inhibition of prostaglandin-degrading enzyme 15-PGDH rejuvenates aged muscle mass and strength

A. R. Palla[1,2], M. Ravichandran[1,2], Y. X. Wang[1,2], L. Alexandrova[4], A. V. Yang[1,2], P. Kraft[1,2], C. A. Holbrook[1,2], C. M. Schürch[2,3], A. T. V. Ho[1,2*], H. M. Blau[1,2†]

Stem-Cell Proliferation

PNAS

Prostaglandin E2 is essential for efficacious skeletal muscle stem-cell function, augmenting regeneration and strength

Andrew T. V. Ho[a,1], Adelaida R. Palla[a,1], Matthew R. Blake[a], Nora D. Yucel[a], Yu Xin Wang[a], Klas E. G. Magnusson[a,b], Colin A. Holbrook[a], Peggy E. Kraft[a], Scott L. Delp[c], and Helen M. Blau[a,2]

Cell Stem Cell

CellPress

Article

Multiomic profiling reveals that prostaglandin E2 reverses aged muscle stem cell dysfunction, leading to increased regeneration and strength

Yu Xin Wang,[1,2,12] Adelaida R. Palla,[1,12] Andrew T.V. Ho,[1,8,12] Daniel C.L. Robinson,[1] Meenakshi Ravichandran,[1] Glenn J. Markov,[1] Thach Mai,[1] Chris Still II,[3,10] Akshay Balsubramani,[4,5] Surag Nair,[4] Colin A. Holbrook,[1] Ann V. Yang,[1] Peggy E. Kraft,[1] Shiqi Su,[1,2] David M. Burns,[1,11] Nora D. Yucel,[1] Lei S. Qi,[6,7,8] Anshul Kundaje,[4,9] and Helen M. Blau[1,13,*]

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

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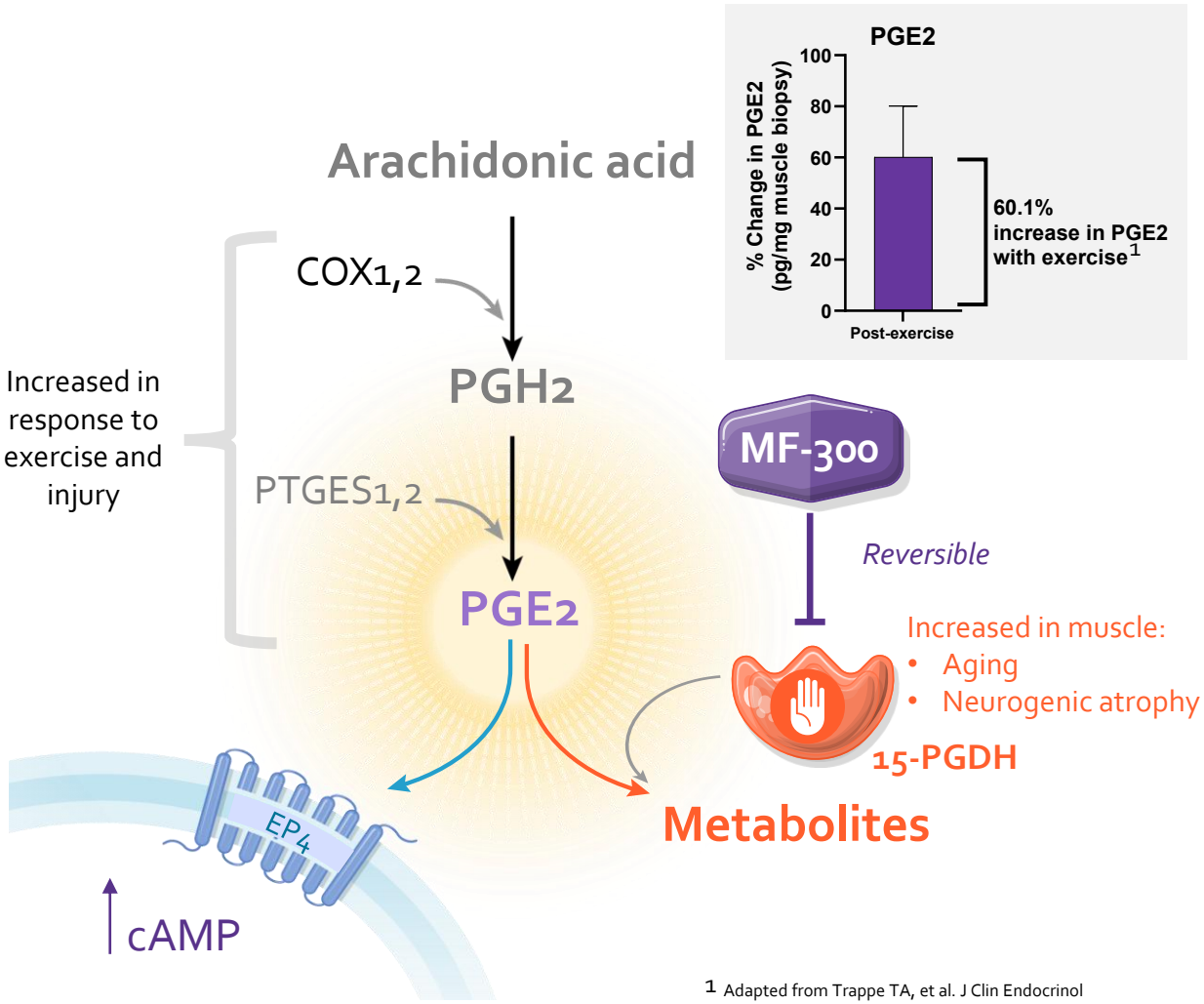
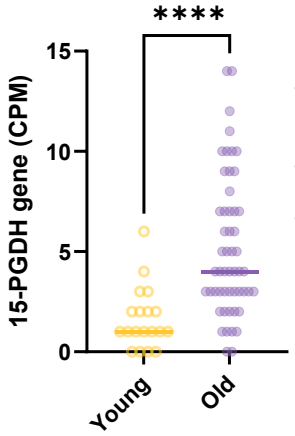
15-HydroxyProstaglandin Dehydrogenase (15-PGDH) Reduces levels of PGE2

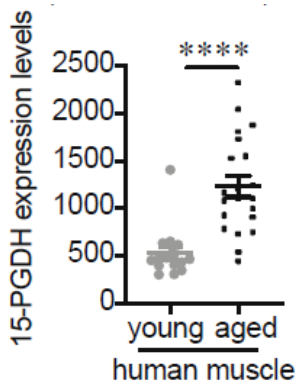


1 Adapted from Trappe TA, et al. J Clin Endocrinol Metab. 2001;86(10):5067-5070

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

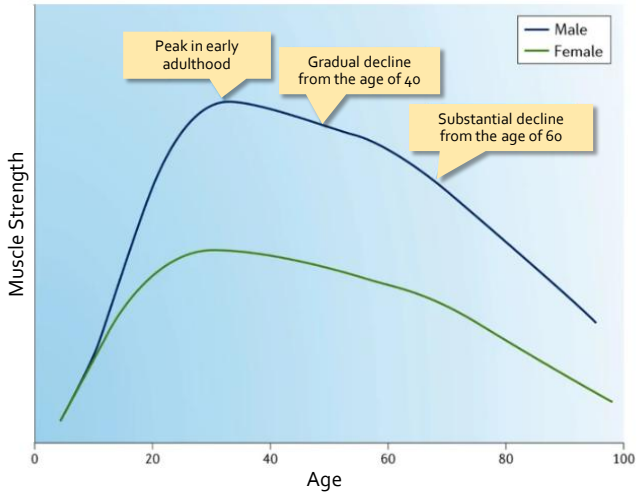


- Vastus lateralis (women and men)
- Young, N = 19 (**25±3 y.o.**)
- Older, N = 29 (**78±6 y.o.**)



- 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]



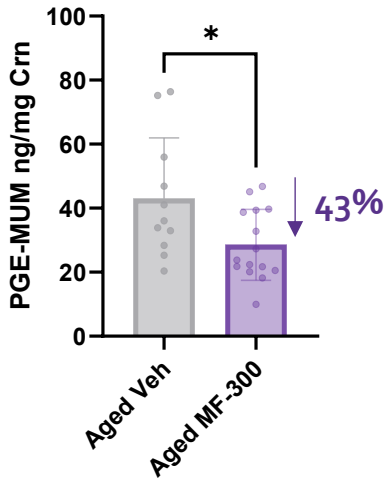
3 GEO167186, 4 Raue et al., *J Appl Physiol* 2012 (published in Palla et al., *Science* 2021), 5 Dennison et al., *Nat Rev Rheum* 2017

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

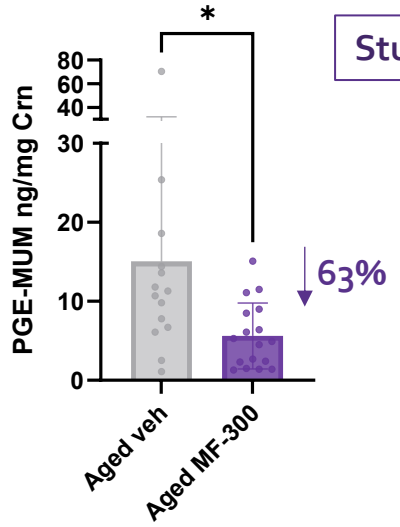
Study 1



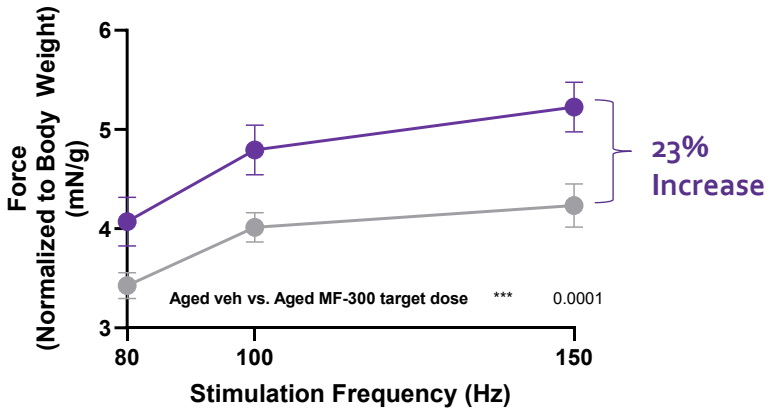
Vehicle
MF-300 target dose mg/kg

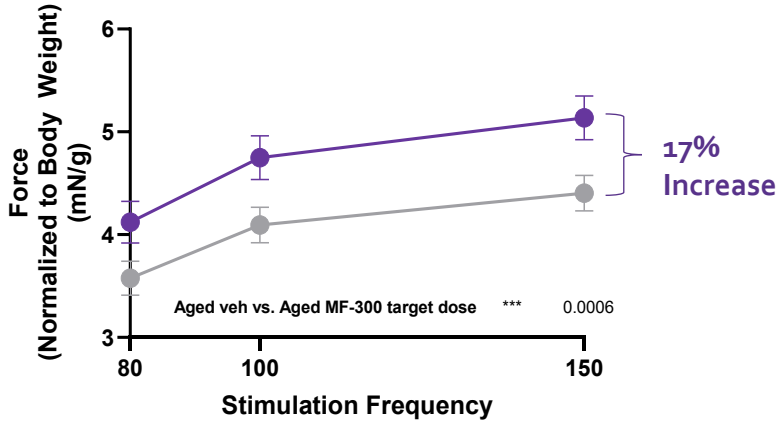
PGE-MUM
↓ ~50% average

Force
↑ ~20% average



Study 2





Target Engagement Biomarker

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

Phase 1 Proof of Mechanism Study

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

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

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

Part 1a SAD

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

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

Part 1b Food Effect

- N=12 (all MF-300)
- 500mg MF-300 administered in the fed or fasted state

Food Effect
2 sequence 2 period cross-over

Part 2 MAD

- N=10 per cohort (2 pbo, 8 MF-300)
- Daily dosing for 5 days to achieve steady state PK
- Doses: 75mg, 125mg, 200mg

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

Phase 1 Clinical Success Criteria to Enable Phase 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

Epirium Bio

MF-300's Safety Profile Supportive of Continued Development

Safe and well tolerated across the evaluated dose ranges

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

Adverse Events: No dose-limiting Toxicities

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

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

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

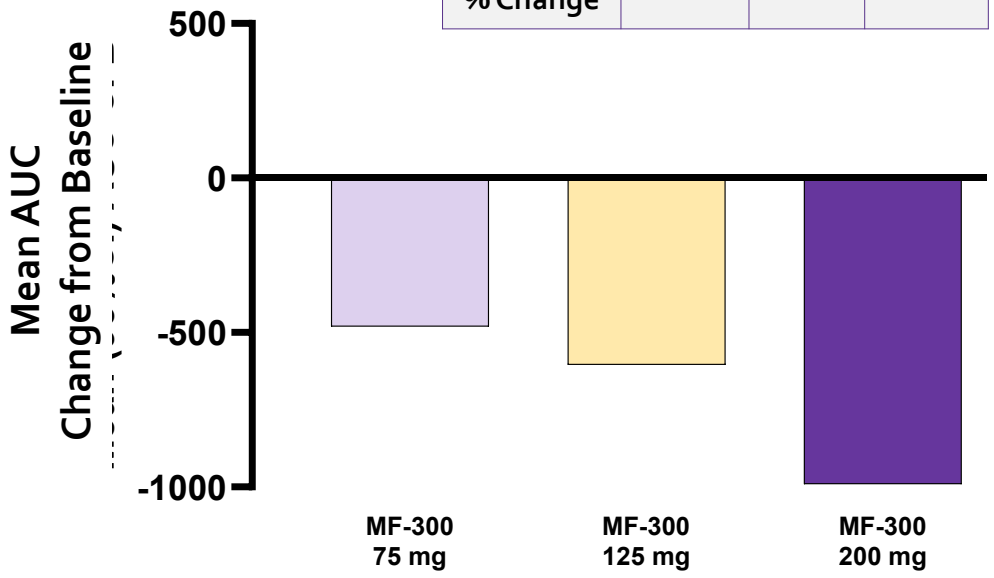
No additional monitoring required beyond standard Phase 2b assessment

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)

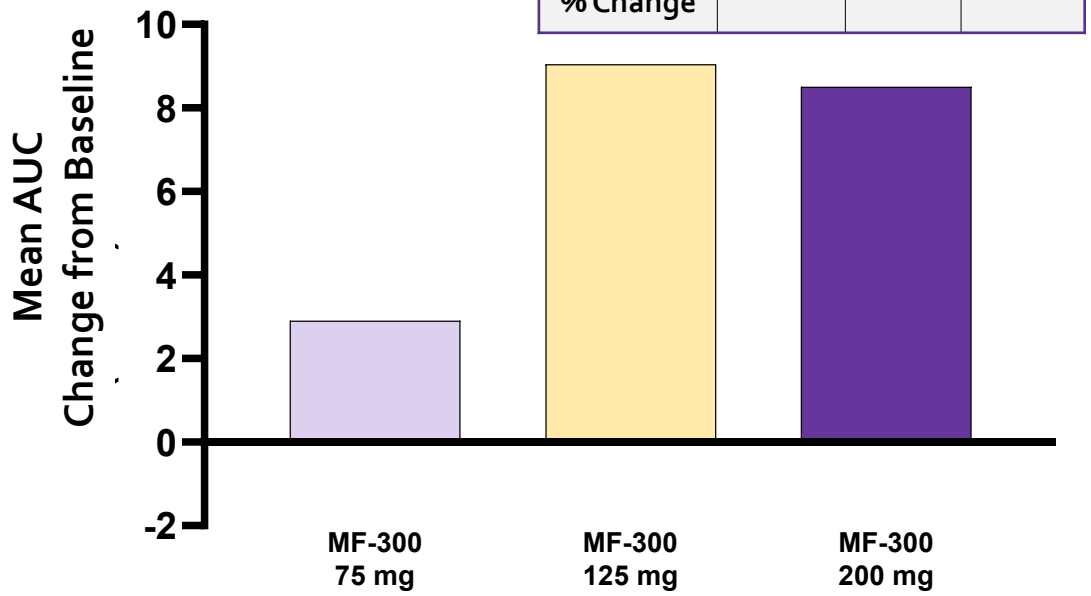
MF-300 (mg)	75	125	200
Placebo Adj. % Change	-64%	-64%	-83%*



*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.

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

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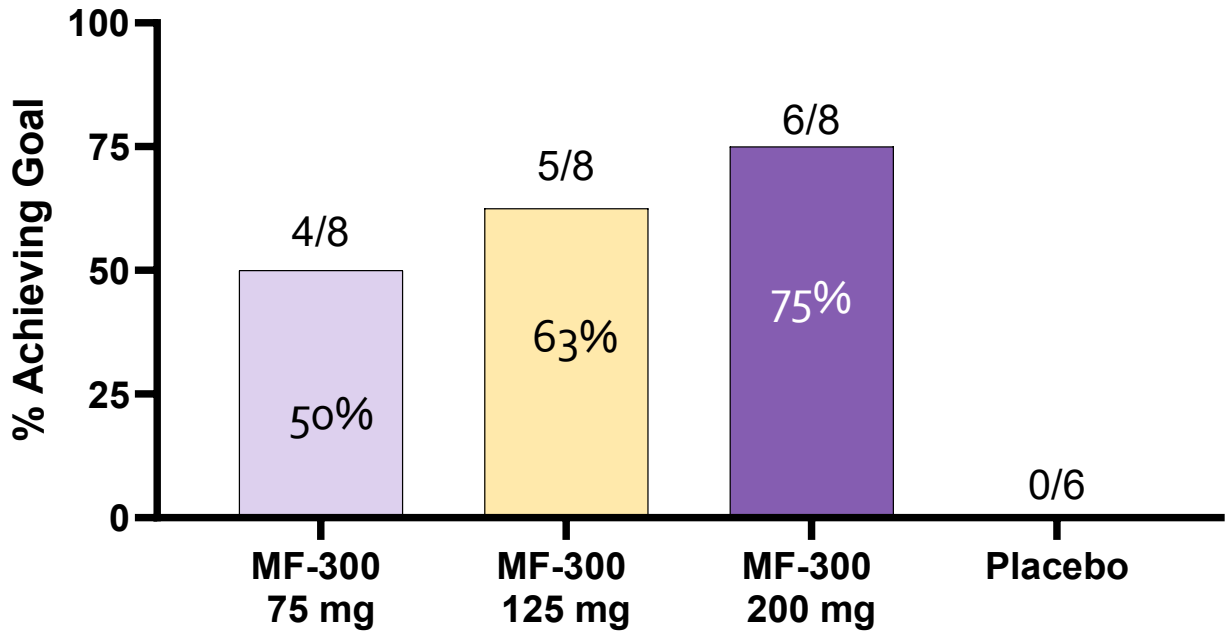
Proportion of Subjects Achieving Targeted % decrease in PGE-MUM & 60% Increase in PGE2



Rationale for targets:

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

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

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

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

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

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

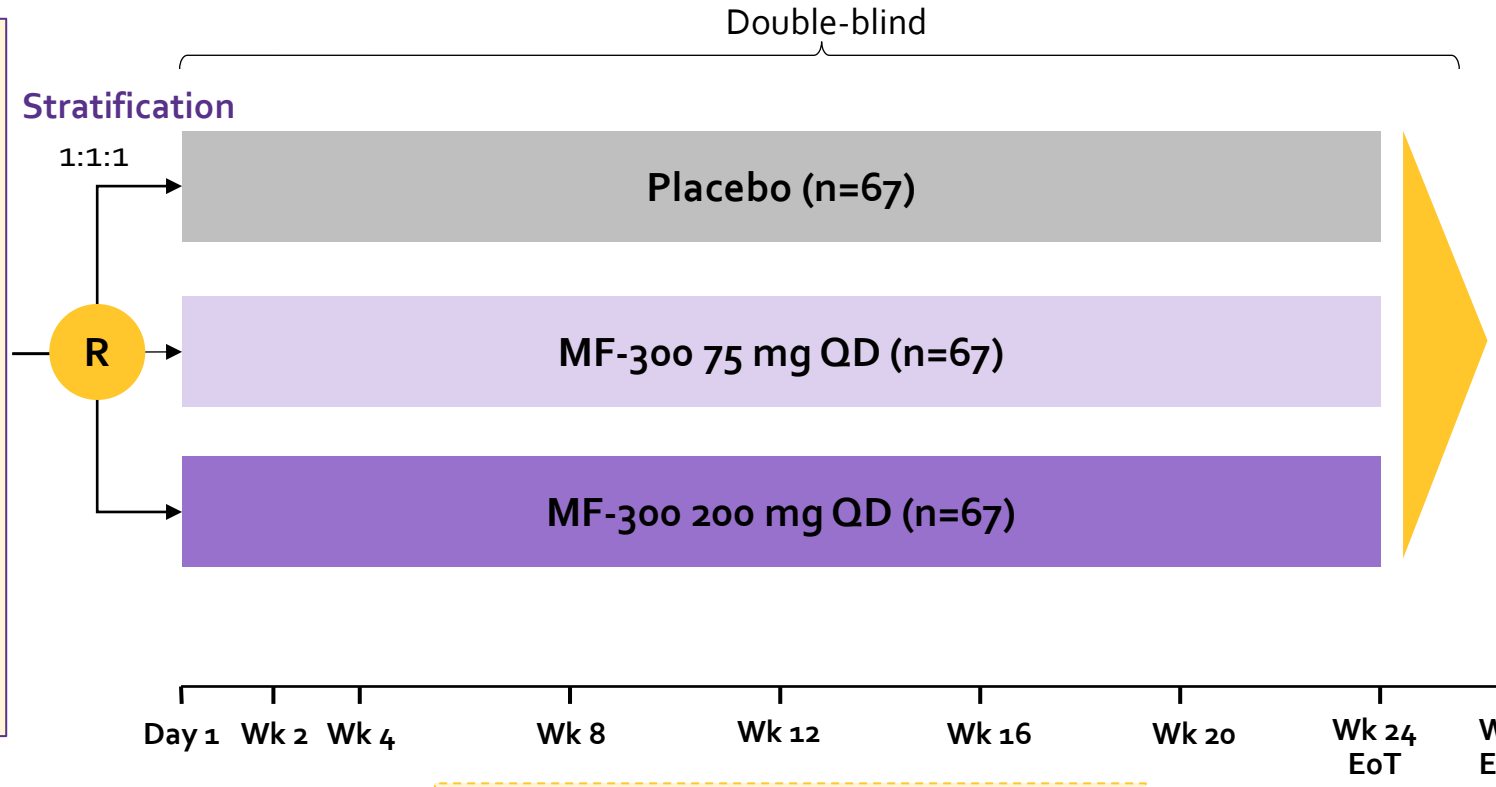
&

- Slowness (walking speed <0.8 m/s)

SPPB Score 4 – 8

5x CST (13.7 – 60 sec)[2]

- Enrich for Poor Performance (>16.7 sec)



Primary Endpoint:

- 5x Chair Stand Test

Key secondary endpoints:

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

Screening (≤4 weeks)

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

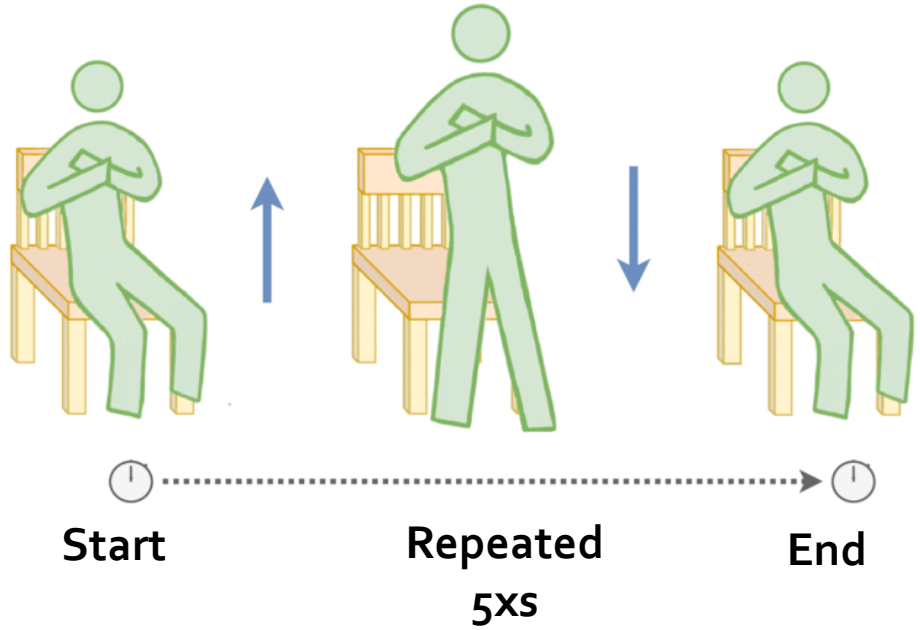
DMC=Data Monitoring Committee; EoT=end of treatment; EoS=end of study; R=randomization; SDOC=Sarcopenia Definitions and Outcomes Consortium; SPPB=Short Physical Performance Battery; Wk=week; yo=years old

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).

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

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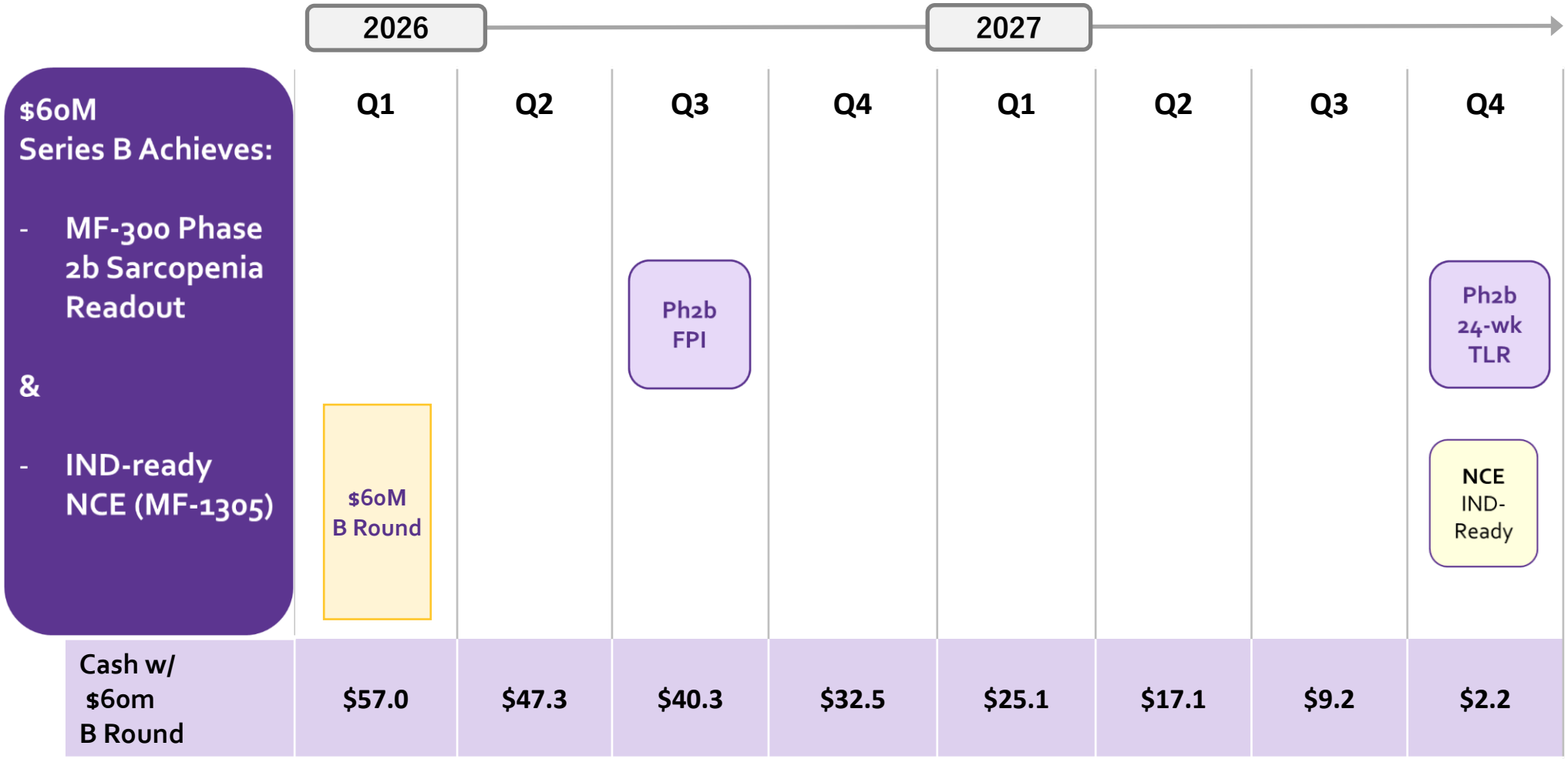

Additional $25M ($85M raise) enables Phase 3 CMC commencement bringing forward MF-300 Commercial Launch 6 months to 1H 2032

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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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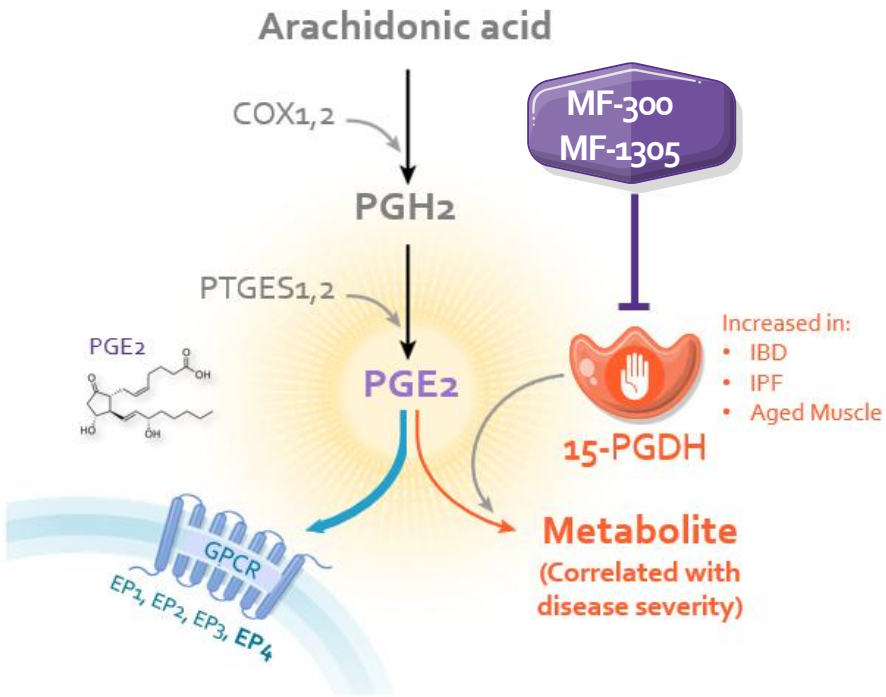
The PGE2/EP4 axis improves outcomes in DSS colitis models

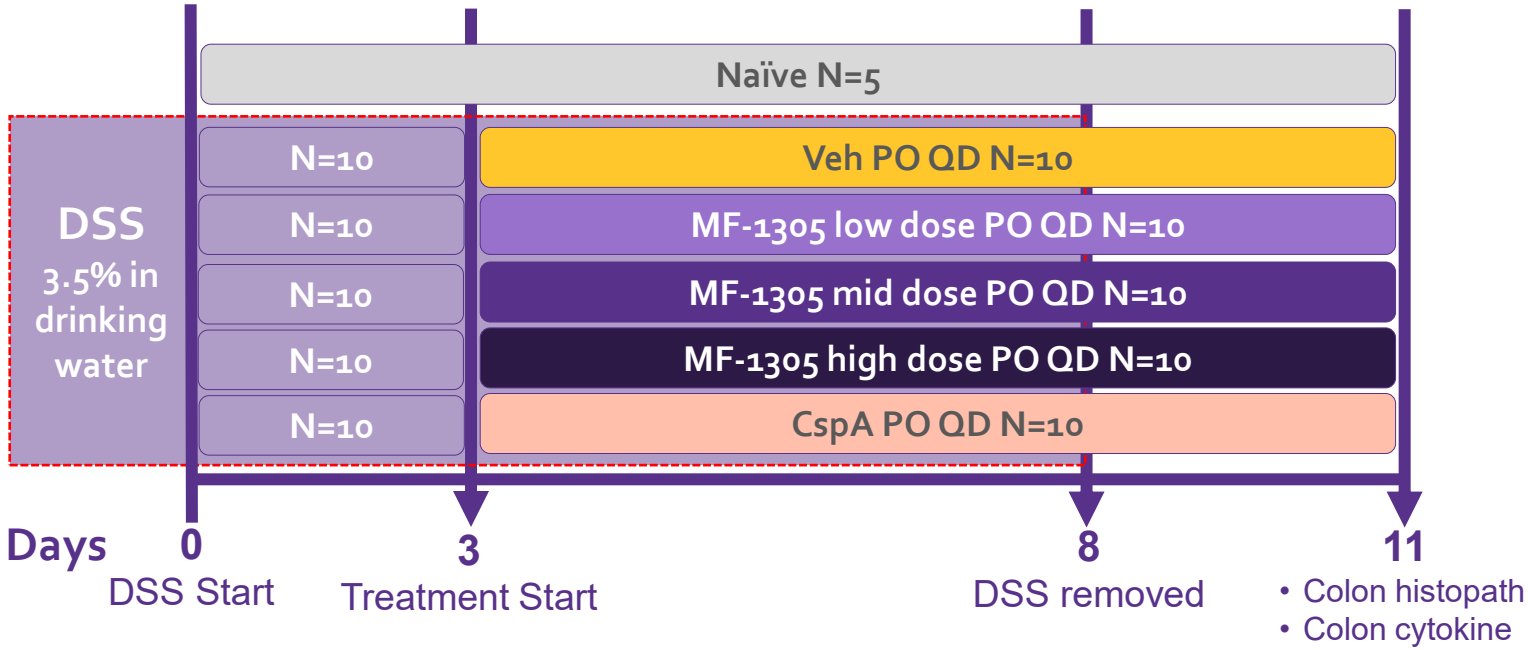


↓ Inflammation
↑ Mucosal protection/healing

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
PGE_2 (Exogenous)	Mouse, DSS colitis	• Alleviated mucosal injury • Promoted epithelial protection/healing	Peng et al. 2017

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

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



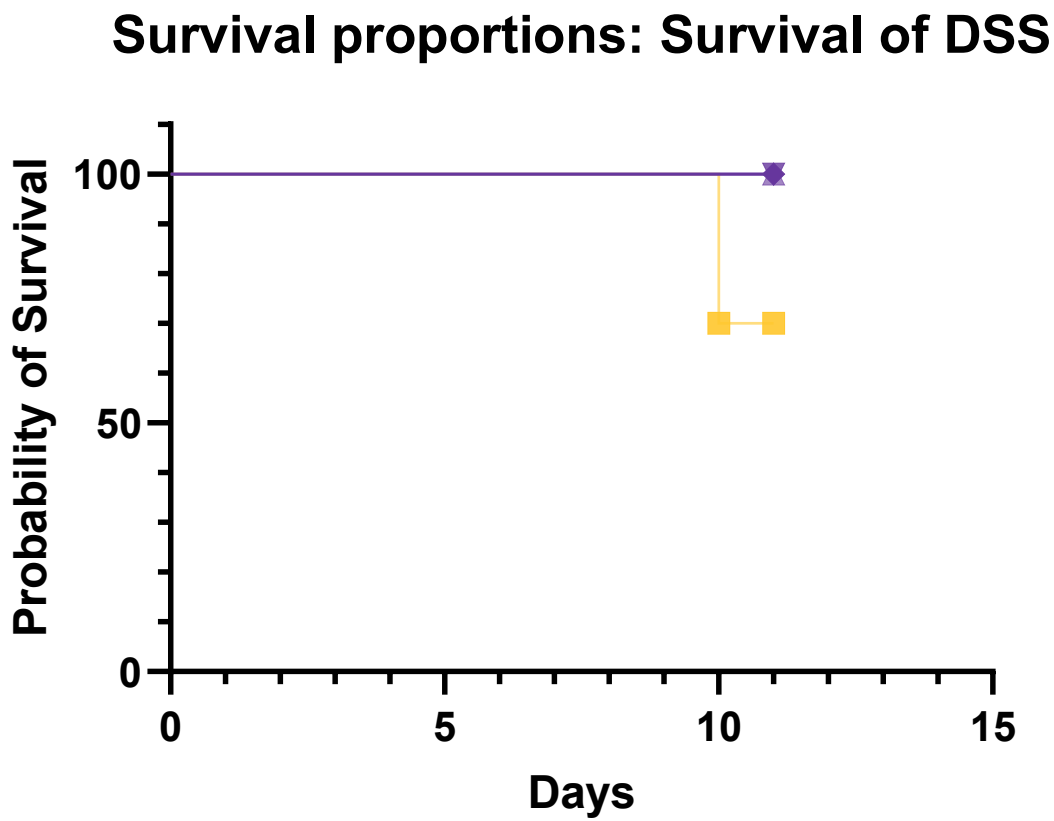
In life:

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

Endpoints:

- Colon
  - Cytokines
  - Histology

MF-1305 Significantly Improved Survival:



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

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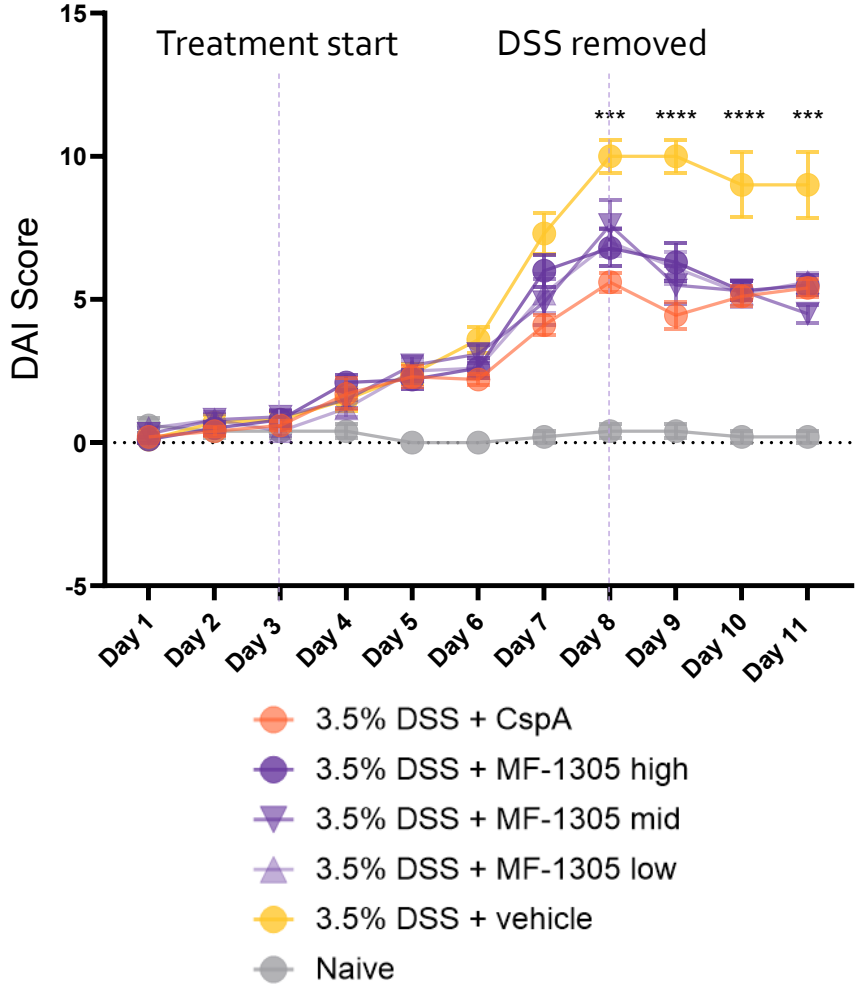
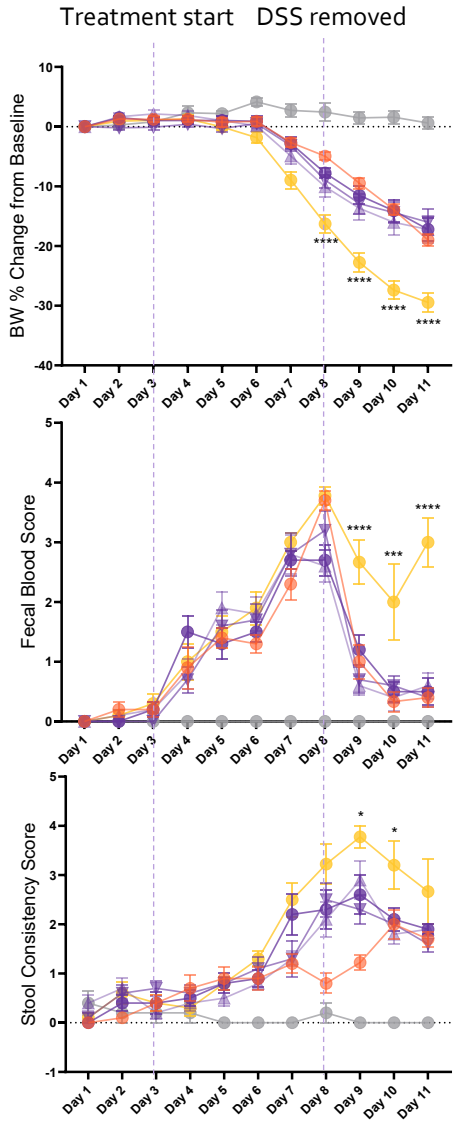
MF-1305 improved DAI



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 improved each composite score of the DAI

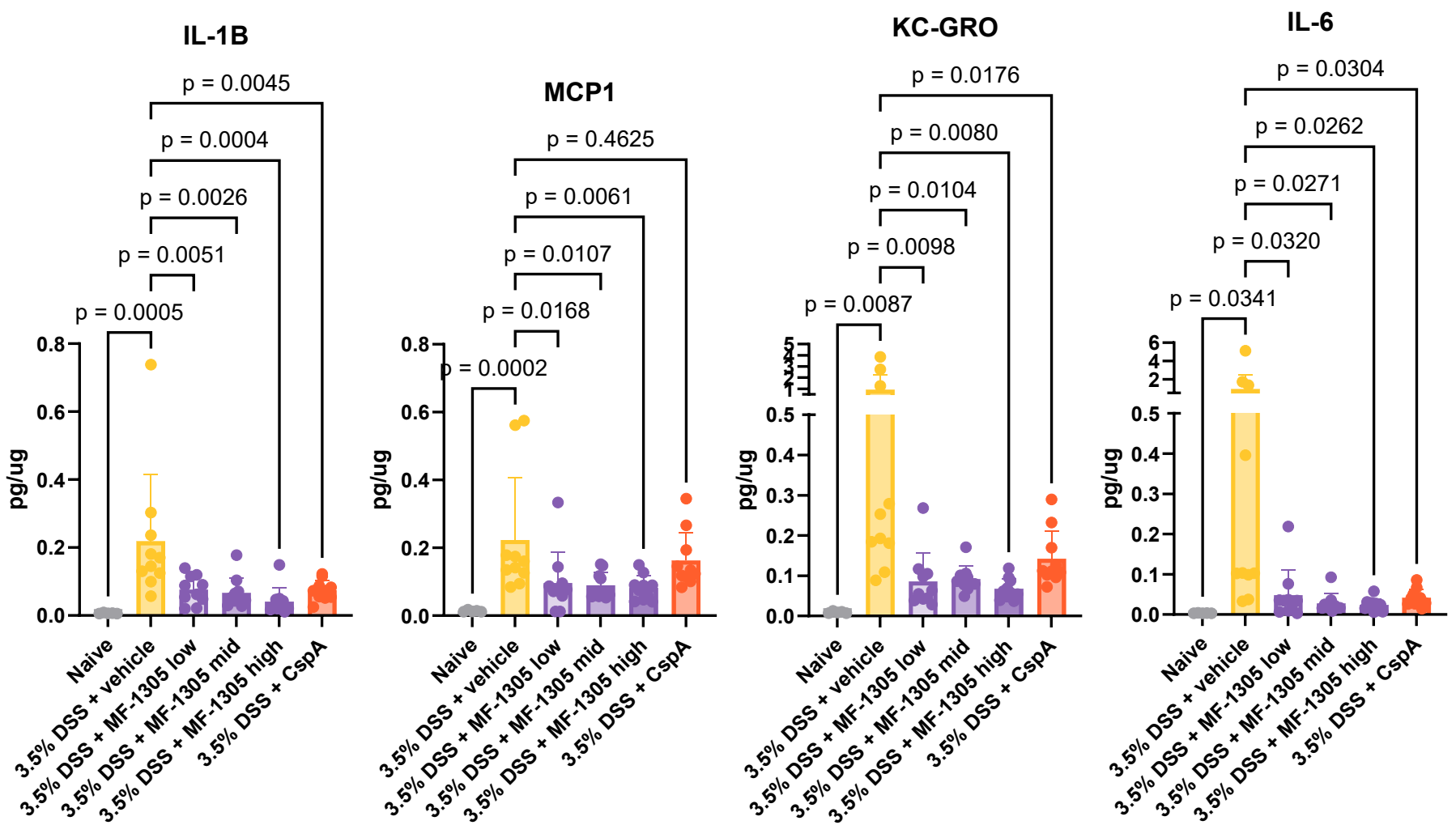


MF-1305 **preserved body weight**

MF-1305 **reduced fecal blood content**

MF-1305 **improved stool consistency**

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

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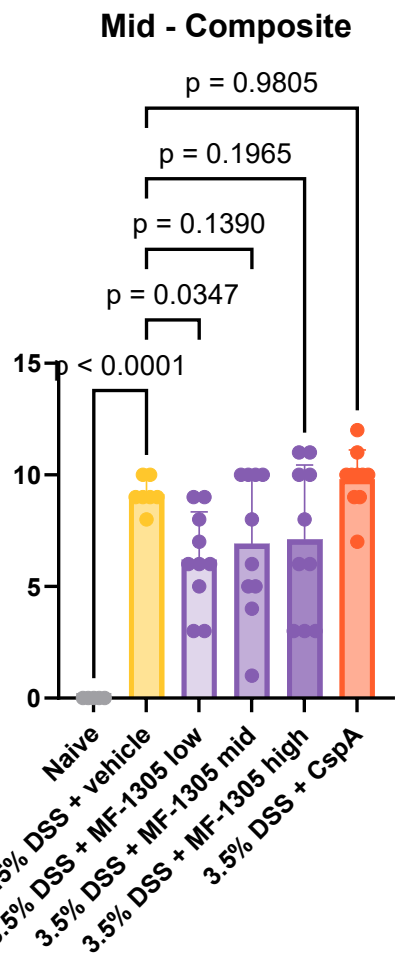
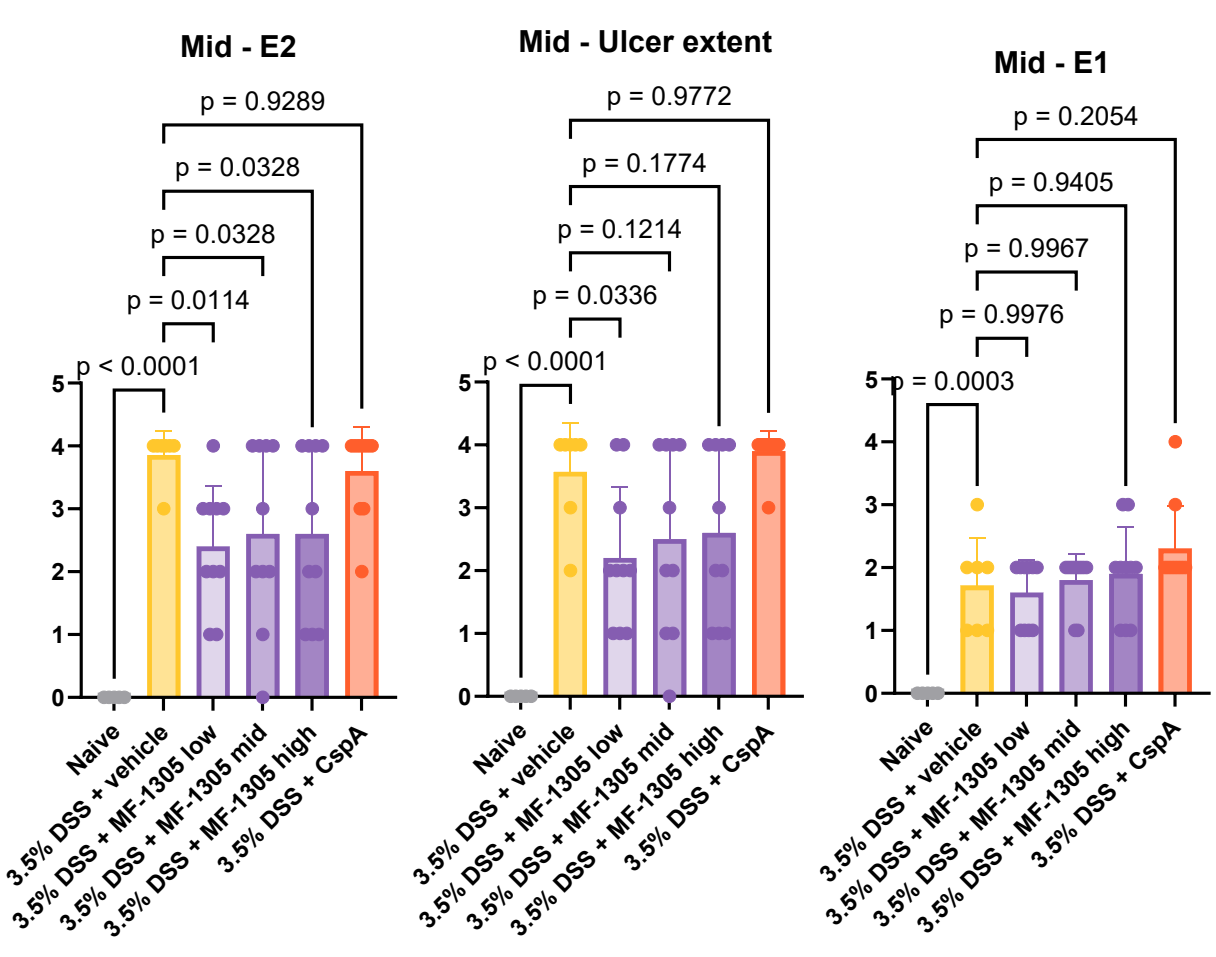
Benefits observed on tissue architecture (i.e., E2) and ulcer extent

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	





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

Key Take-Aways: Supporting Therapeutic Potential of 15-PGDH Inhibition for IBD

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.