

MF-300 (15-PGDH Enzyme Inhibitor) Reverses Age-Related Muscle Weakness in Mice by Restoring Muscle Quality

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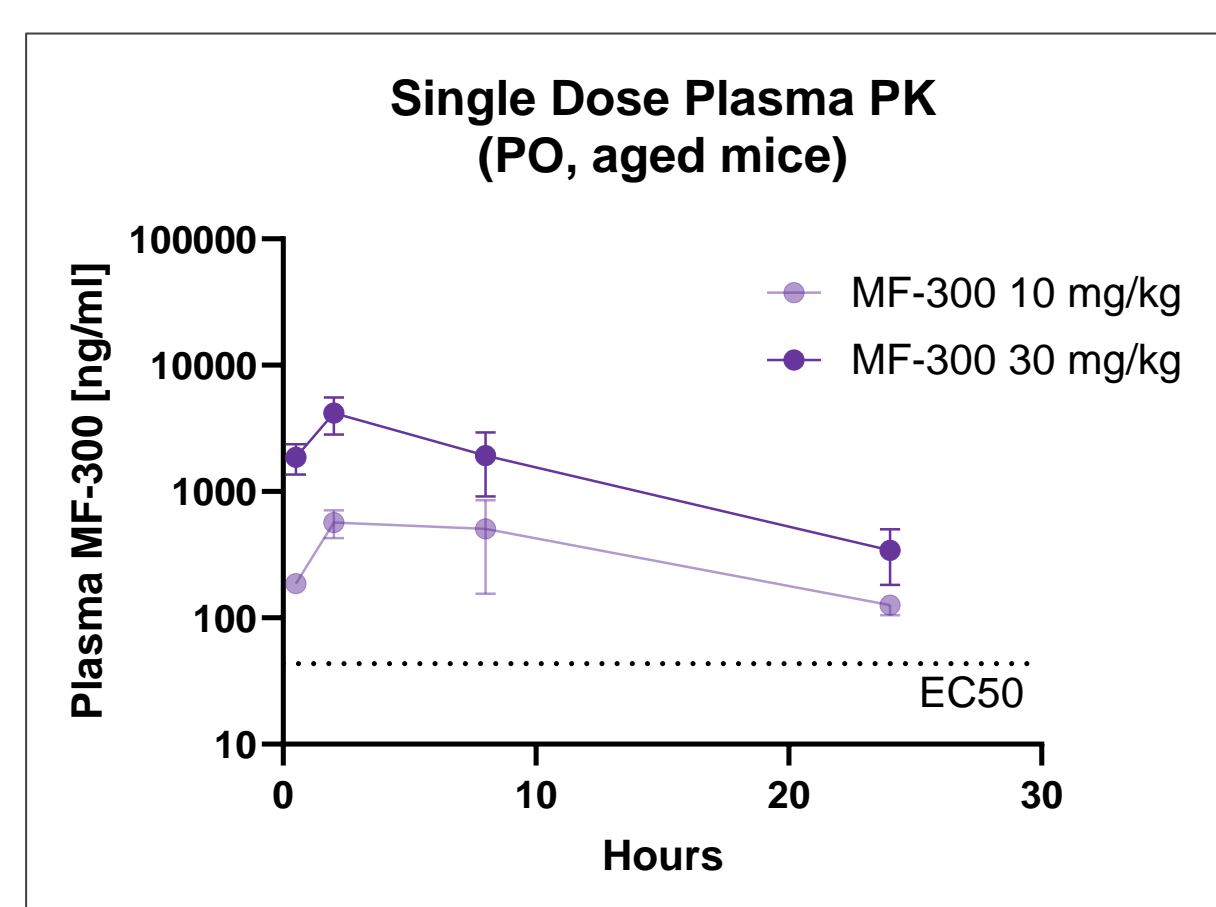
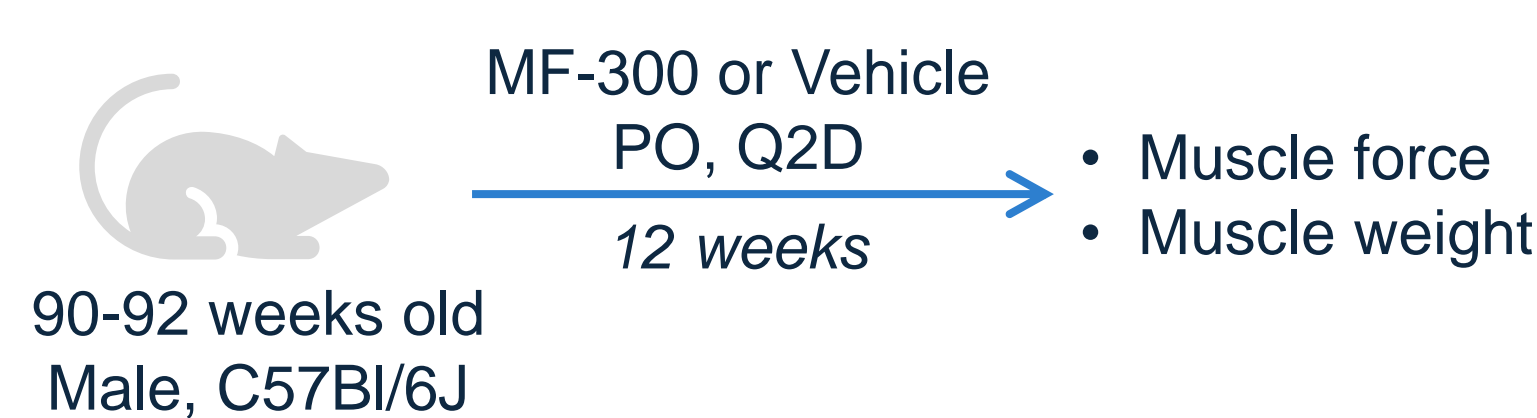
Introduction:

- Sarcopenia, age-induced muscle weakness, is caused by reduced muscle quality and muscle quantity and disproportionately affects fast-twitch muscle.
- Muscle force and rate of contraction are reduced in sarcopenia.
- Improving quality of fast-twitch muscle in aging is a strategy to enhance strength and offset progression of sarcopenia.
- Prostaglandin E2 (PGE2) improves muscle function in aged mice^{1,2}.
- MF-300, an oral inhibitor of the enzyme, 15-hydroxyprostaglandin dehydrogenase (15-PGDH), increases levels of PGE2 in muscle and improves muscle quality and force in aged mice.

Methods:

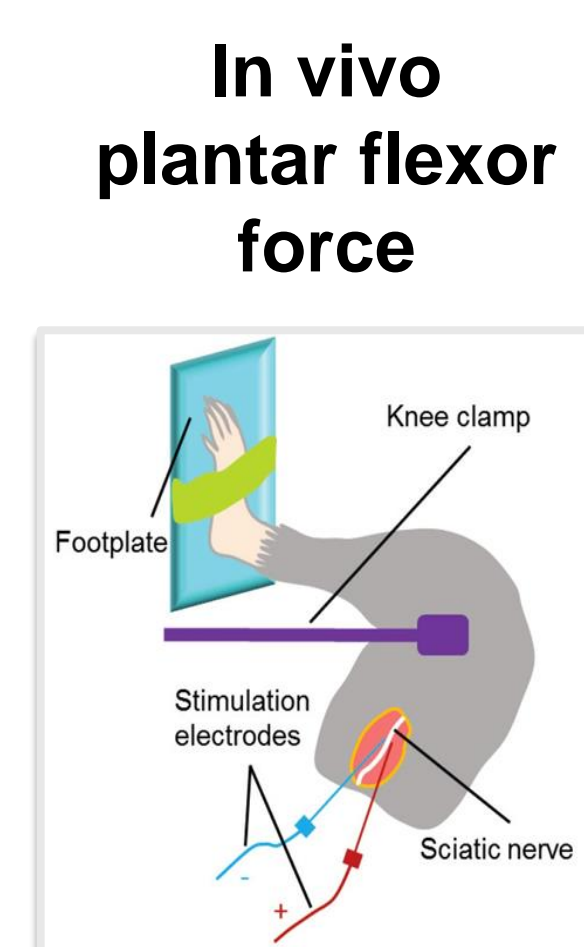
- Male mice, C57Bl/6J, 90-92 weeks old (aged) or 39-54 weeks old (adult)
- N = 18 / grp aged, N = 15 / grp adult
- MF-300 or vehicle was administered orally, every other day for 12 weeks
- Muscle force was measured in vivo (isometric plantar flexion) or ex vivo (isometric force of the extensor digitorum longus (EDL) muscle) with a 305C muscle lever system (Aurora Scientific Inc., Aurora, CAN)
- Statistical analyses: One-Way ANOVA with a Holm-Šidák post-hoc or a Two-Way Repeated Measures ANOVA with a Holm-Šidák post-hoc, or Students t-Test for pairwise comparisons

Study design:

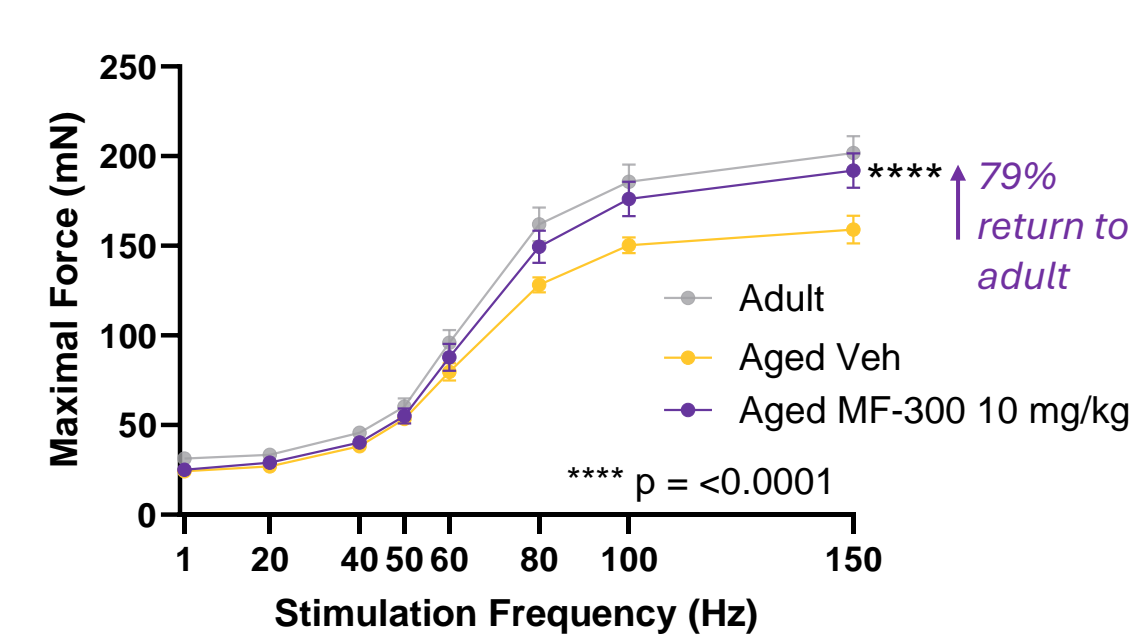


Key Results:

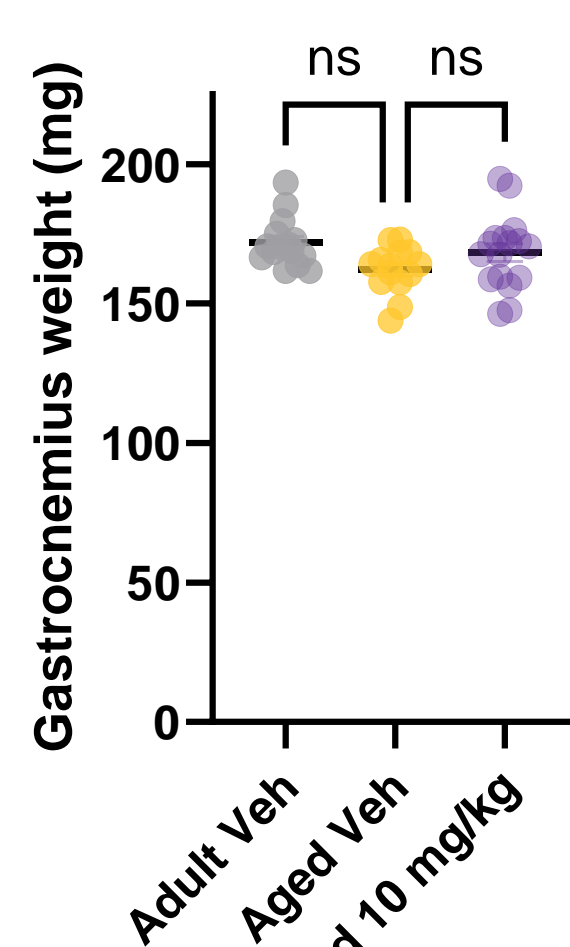
- MF-300 increased aged absolute and specific force (force/muscle weight), in vivo



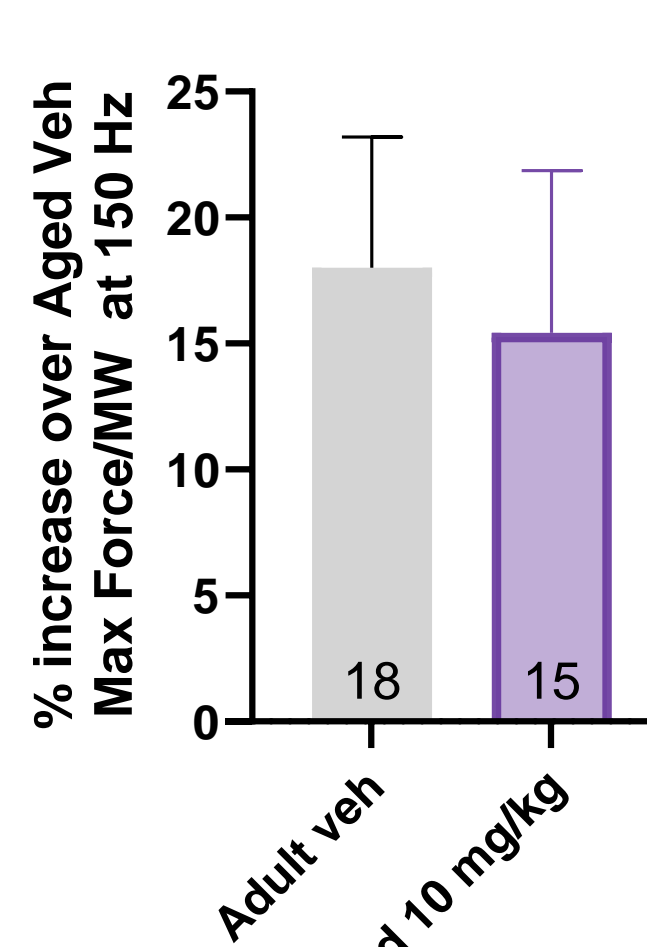
Increased absolute force



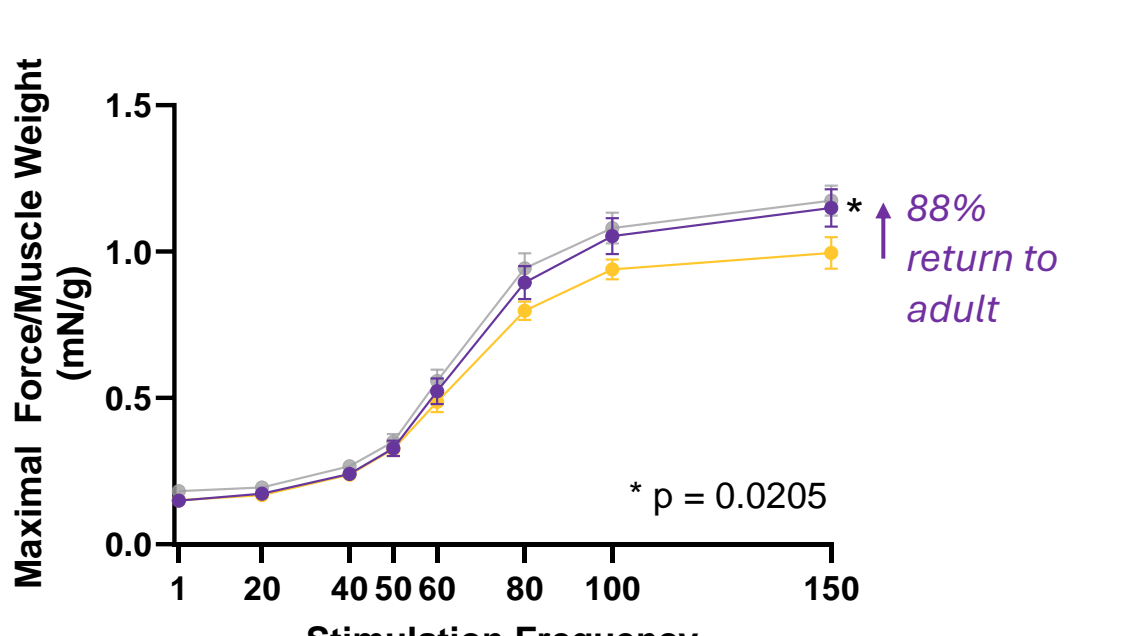
No effect on muscle mass



15% increase in specific force



Increased specific force

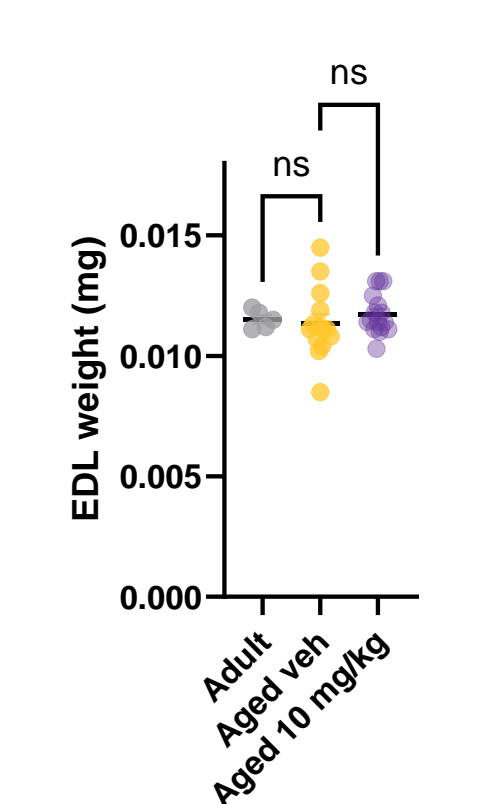


- MF-300 increased specific force and contraction rate in clinically relevant fast-twitch muscle of the EDL, ex vivo

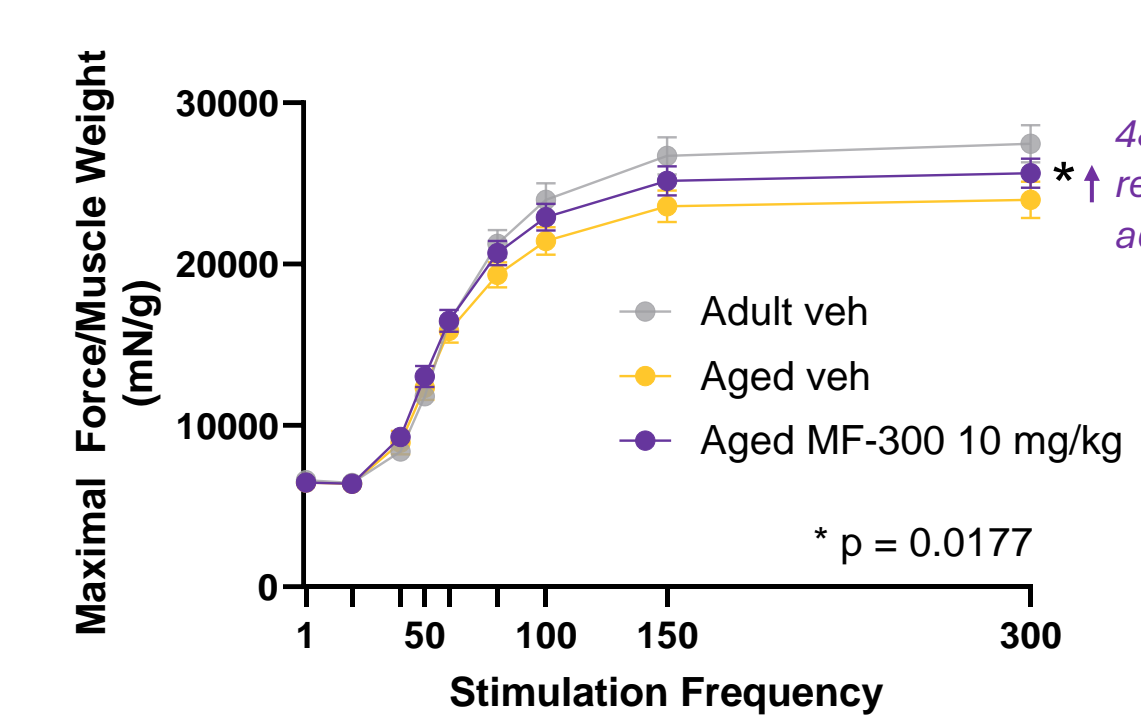
Ex vivo EDL force



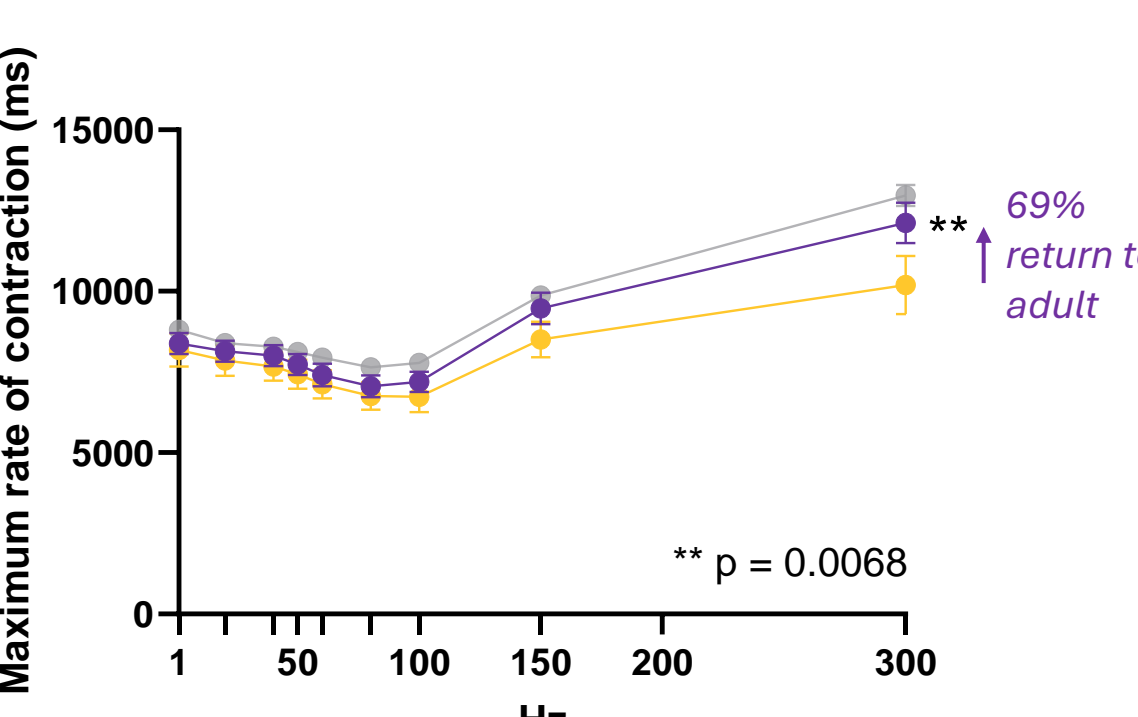
No effect on muscle mass



Increased specific force



Increased contraction rate

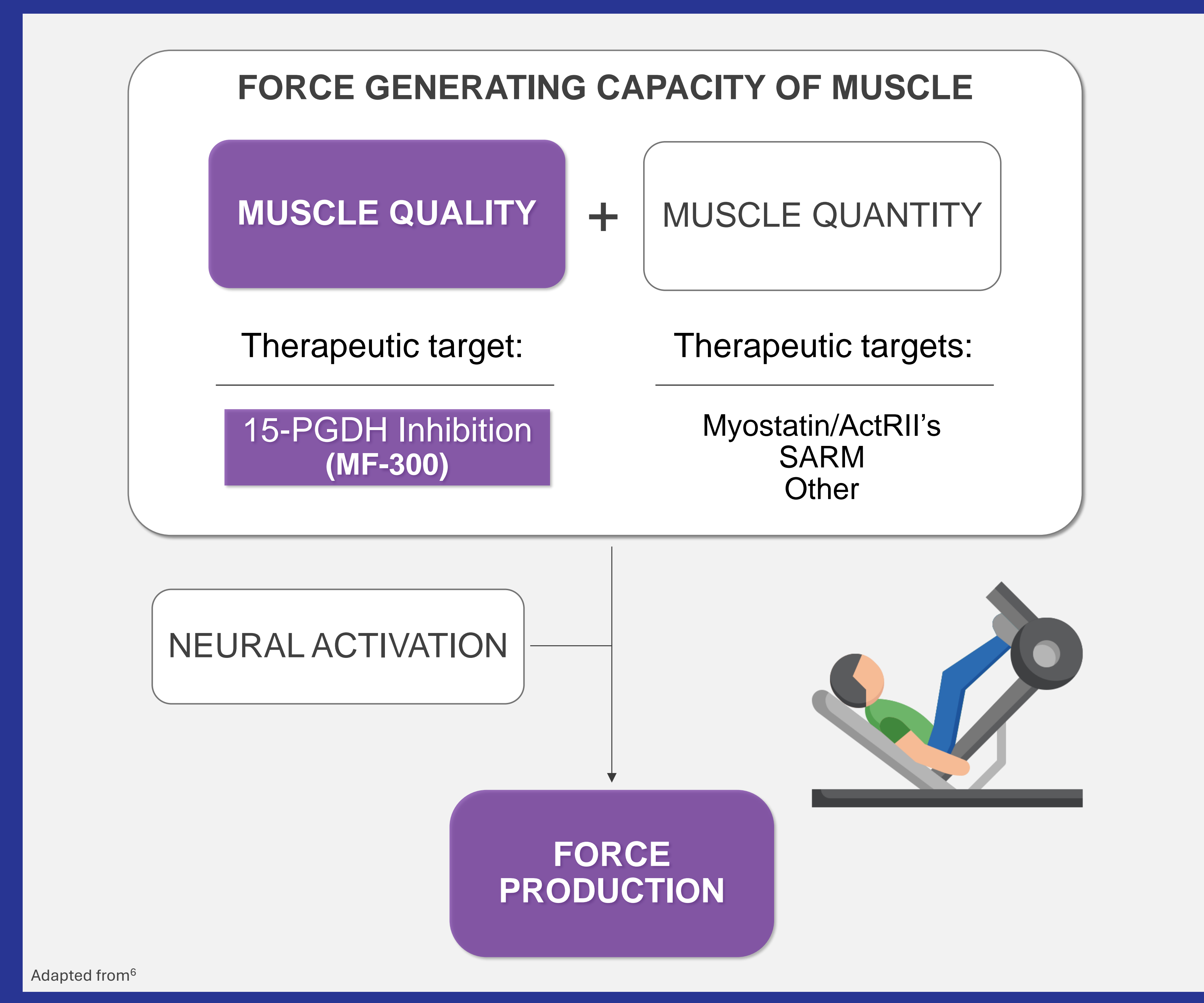


- Sarcopenia -

- Substantial and rapidly growing unmet need
 - No FDA approved therapy
- Caused by reduction in muscle quality (intrinsic force generating capacity of muscle) and muscle quantity

- MF-300 -

- Oral inhibitor of the enzyme, 15-PGDH
- Increases Prostaglandin E2 in muscle
- Increases muscle force and improves muscle quality in aged mice
 - Ph 1 readout in Healthy Volunteers 2nd half of 2025



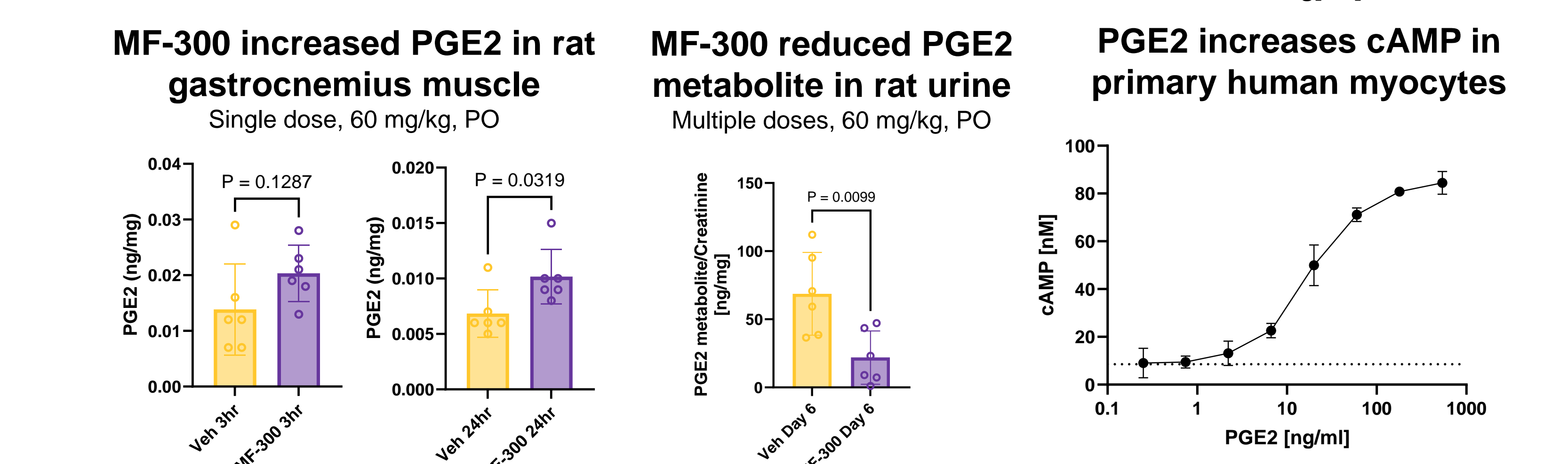
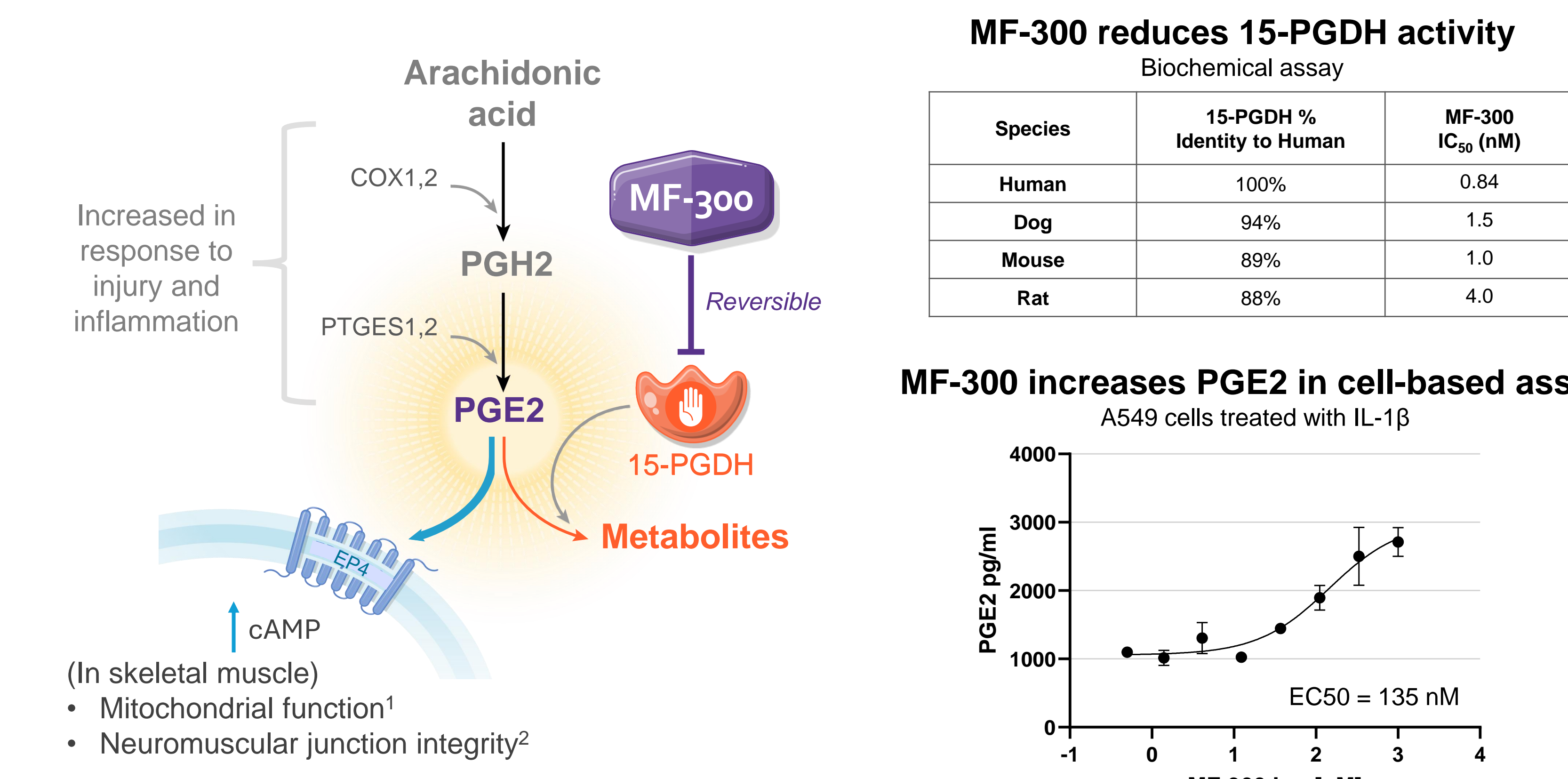
Financial Disclosure: This research is funded by Epirium Bio.

Discussion:

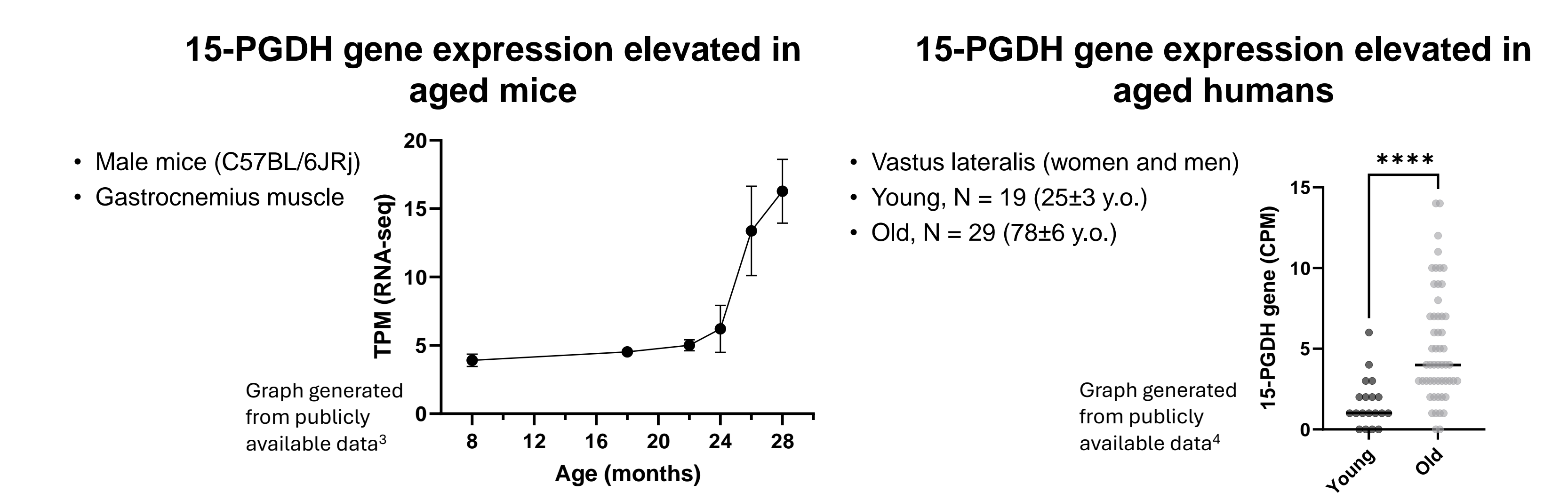
- Oral administration of MF-300 reversed age-induced reduction of absolute and specific muscle force, as well as contraction rate, in clinically relevant fast-twitch muscle.
- MF-300 increased force without increasing muscle mass, suggesting that MF-300 improved the quality of aged muscle.
- Pharmacodynamic biomarkers including PGE2 and a PGE2 metabolite support in vivo target engagement of MF-300 with 15-PGDH in the target tissue, skeletal muscle (see Supporting Information, below).

Supporting Information:

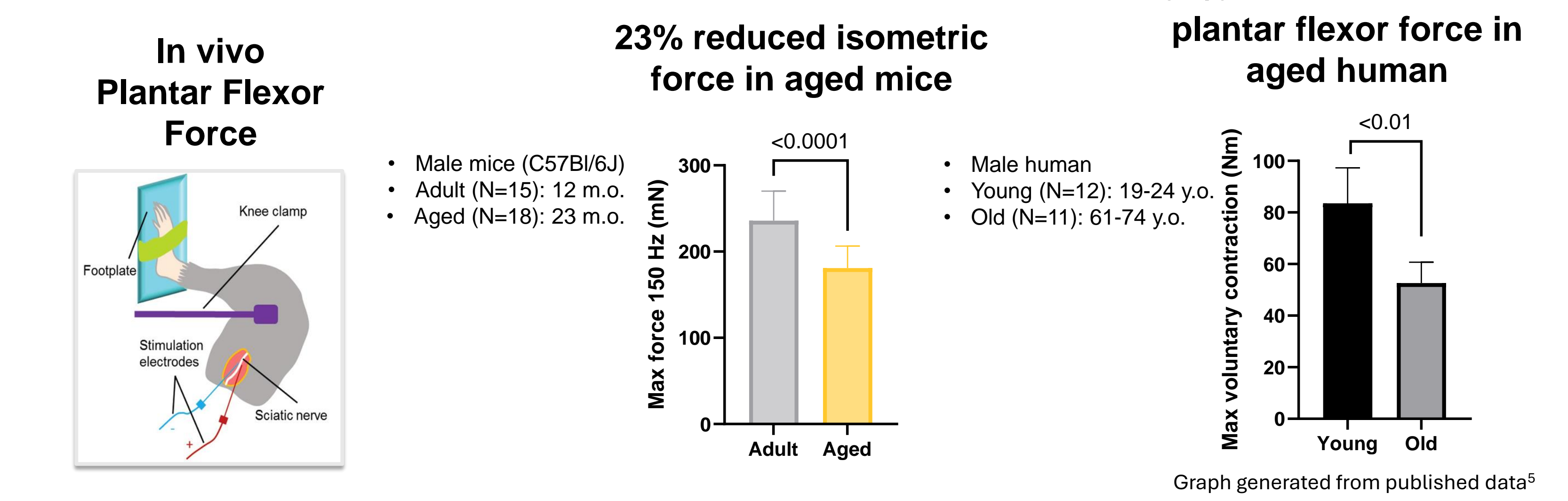
- MF-300 inhibits 15-PGDH and increases levels of PGE2



- 15-PGDH gene expression is elevated in muscle with aging in mouse and human



- Mouse isometric plantar flexor force as a translational endpoint for age induced muscle weakness in human



References:

- Palla et al., *Science*, 2021
- Bakooshi et al., *Sci. Transl. Med.*, 2023
- <https://sarcoatlas.scicore.unibas.ch/>
- GEO167186 published in Perez et al., *Aging*, 2022
- Ochala et al., *Exp Ger*, 2004
- Jubrias and Conley, *Fun. Neurobio. of Aging*, 2001

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Acknowledgements: We thank Andrew Ho, PhD, for contributions to data analysis and thought partnership, Elaine Chiquette, PharmD, for literature research and contributions to Epirium's communication efforts, Siva Lavu, PhD, for supporting bioanalytical activities. We thank the talented CRO's and vendors who contributed to study operations and sample analysis including HD Bio (San Diego, CA), Nextcea (Woburn MA), ZenBio (Durham, NC), and Unites (Madison, WI).

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