Phase 1 Evaluation of MF-300: An Investigational First-in-Class Oral Candidate for Sarcopenia

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Introduction

- Age-related sarcopenia is a progressive chronic disease that leads to a loss of skeletal muscle mass and function, contributing to disability and loss of independence.[1]
- Despite being associated with increased falls, hospitalization, and all-cause mortality, there is no approved pharmacologic treatment for sarcopenia, representing an important unmet medical need.[1,2]
- MF-300 is a first-in-class orally administered 15-hydroxyprostaglandin dehydrogenase (15-PDGH) small molecule inhibitor. MF-300 prevents prostaglandin E2 (PGE_2) metabolism by 15-PGDH, increasing muscle PGE_2, and consequently cyclic adenosine monophosphate (cAMP), to physiological levels.[3,4]
- MF-300 has demonstrated an ability to improve muscle force in preclinical studies and is currently in development for treatment of adults living with sarcopenia.[5]

Study design and objectives

- **This Phase 1 double-blind single ascending dose (SAD) and multiple ascending dose (MAD) study evaluated the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of MF-300 in healthy adults.**
- Cohorts of healthy adults aged 18–65 years were dosed with MF-300 or placebo (pbo) per the schematic below.

Part 1 SAD
- N=8 per cohort (2 pbo, 6 MF-300)
- Doses: 75, 125, 250, 500, 800 mg

Single Ascending Dose
5 adult cohorts

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

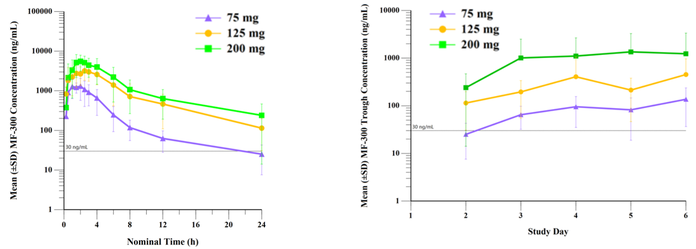
Multiple Ascending Dose
3 adult cohorts

Baseline demographics

		MF-300 Total active N=54	Pbo N=16
Sex, n (%)	Female	28 (51.9)	9 (56.3)
	Male	26 (48.1)	7 (43.8)
Age (years)	Mean (SD)	37.0 (10.1)	37.2 (11.6)
	Median	37.5	35.0
	Min, max	19, 61	24, 58
BMI (kg/m^2)	Mean (SD)	25.5 (2.8)	25.7 (3.6)
	Median	25.6	25.4
	Min, max	18.8, 30.8	18.4, 32.2
Ethnicity, n (%)	Hispanic or Latino	17 (31.5)	7 (43.8)
	Other	37 (68.5)	9 (56.3)
Race*, n	White	34	7
	Black or African American	19	9
	Other	2	1

** Subjects may select more than one; BMI, body mass index; max, maximum; min, minimum; SD, standard deviation*

MF-300 exposure is dose-dependent with fast absorption and a consistent half-life



- PK evaluation of the MAD cohorts demonstrated rapid absorption (mean [SD] T_{max} 1.5 [0.9], 2.4 [1.8], and 2.3 [1.1] hours [h]), dose-dependent exposure (mean [SD] C_{max} 1820 [843], 4070 [1160], and 6230 [2590] ng/mL) for 75, 125, and 200 mg MF-300, respectively.
- PK evaluation of the SAD cohorts showed a consistent half-life ranging from 12.2–15.9 hours (h).
- Steady state was achieved by day 3–4, with a modest accumulation ratio (area under the curve [AUC] 1.3–1.6x).
- Exposure increased in a more than dose-proportional manner, particularly at steady state but less so at higher doses (125–250 mg).

MF-300 was well tolerated with no SAEs or discontinuations due to AEs

SAD cohorts: summary of AEs

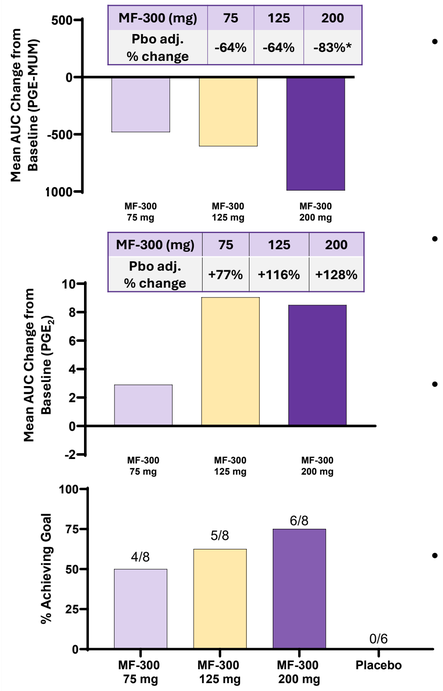
System Organ Class preferred term n, (%), events	MF-300 75 mg N=6	MF-300 125 mg N=6	MF-300 250 mg N=6	MF-300 500 mg N=6	MF-300 800 mg N=6	Total active N=30	Pbo N=10
Subjects with any TEAE							
	4 (66.7) 6	3 (50.0) 3	5 (83.3) 16	1 (16.7) 1	3 (50.0) 7	16 (53.3) 33	0
≥2 subjects with any TEAE							
Diarrhea	3 (50.0) 3	1 (16.7) 1	2 (33.3) 2	1 (16.7) 1	2 (33.3) 2	9 (30.0) 9	0
Nausea	0	0	2 (33.3) 2	0	0	2 (6.7) 2	0
Dermatitis contact	0	0	2 (33.3) 2	0	1 (16.7) 1	3 (10.0) 3	0
Intermenstrual bleeding	0	0	0	0	2 (33.3) 2	2 (6.7) 2	0
Headache	0	0	1 (16.7) 1	0	1 (16.7) 1	2 (6.7) 2	0

MAD cohorts: summary of AEs

System Organ Class preferred term n, (%), events	MF-300 75 mg N=8	MF-300 125 mg N=8	MF-300 200 mg N=8	Total active N=24	Pbo N=6
Subjects with any TEAE					
	3 (37.5) 3	1 (12.5) 2	3 (37.5) 7	7 (29.2) 12	2 (33.3) 3
≥2 subjects with any TEAE					
Dysmenorrhea	0	0	2 (25.0) 2	2 (8.3) 2	0

AE, adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

MF-300 treatment leads to reduced PGE-MUM and increased PGE_2



- Target engagement was evaluated by quantifying urine levels of PGE_2 and its urinary metabolite, prostaglandin E-major urinary metabolite (PGE-MUM).
- MF-300 leads to a dose-dependent decrease in PGE-MUM, demonstrating successful target engagement.
- MF-300 leads to a relative increase in PGE_2 consistent with that observed previously following eccentric exercise in humans.[6]
- Following MF-300 treatment, a high proportion of subjects (≥50% for all doses) achieved a ≥50% decrease in PGE-MUM and a ≥60% increase in PGE_2.

**p<0.05 versus placebo. Adj., adjusted*

Conclusions

- PK evaluation showed that MF-300 exposure increases predictably with dose with a consistent half-life and exposures aligned with preclinical efficacy targets
  - These data support a once daily dosing regimen.
- There were no unexpected or dose-limiting safety findings, no SAEs, and no discontinuations due to AEs.
- PD analysis showed evidence of target engagement with over half of the population achieving a ≥50% decrease in PGE-MUM and a ≥60% increase in urinary PGE_2.
- **Overall, all predefined success criteria across PK, safety, and PD were achieved, enabling advancement into Phase 2.**

References

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MF-300 is an investigational product candidate being evaluated for sarcopenia. MF-300 has not been approved by any regulatory authority, and its safety and efficacy have not been established.