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Pharmacology and Clinical Profile of MYMD-1® (isomyosamine), an Oral, Selective, Next-generation, TNFα Inhibitor that Crosses the Blood Brain Barrier

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Background

- MyMD Pharmaceuticals Inc. (MyMD) is developing MYMD-1®, a novel, oral, small molecule therapeutic for the treatment of inflammatory and autoimmune disorders, including rheumatoid arthritis.
- Tumor necrosis factor-alpha (TNFα) is a proinflammatory cytokine that plays a pivotal role in regulating the inflammatory response in chronic autoimmune diseases such as rheumatoid arthritis (RA). The discovery of the role of TNFα in the pathogenesis of RA has led to anti-TNF biological therapies as breakthroughs in the treatment of RA.
- The objective of the studies was to evaluate the potency of MYMD-1® in human peripheral blood mononuclear cells (PBMCs), assess in vivo efficacy in a relevant model of rheumatoid arthritis and evaluate the safety, tolerability and pharmacokinetics in a Phase 1 SAD/MAD clinical trial.

Methods

- In vitro, MYMD-1® was profiled for inhibition of (CD)3/anti-CD28-mediated release of cytokines, including IFN γ, IL-2, IL-10, and TNFα, from human PBMCs
  - At least 6 different MYMD-1 concentrations (≤4 μM) were tested and each determined against 12 human PBMC donor samples.
  - Positive controls were included for comparison: anti-CD3 (clone OKT3), anti-CD28 (clone 28.2), and PHA
- In vivo, MYMD-1® was evaluated in a murine model of Collagen Antibody Induced Arthritis (CAIA), mimicking features of rheumatoid arthritis
  - MYMD-1® dose levels evaluated were 50, 250, and 450 mg/kg/day; Etanercept:10 mg/kg SC Q3D
- In healthy adults subjects, two randomized, placebo-controlled, double-blind studies evaluated safety, tolerability, and pharmacokinetics of single or repeat MYMD-1 once daily (QD) dosing
  - Single-dose escalation study: three cohorts (n=8/cohort; 6 on MYMD-1®; 2 on placebo) received MYMD-1® 150, 300, or 450 mg.
  - Multiple ascending dose study: Cohort 4 (MYMD-1® n=6; placebo n=2) received MYMD-1® 600 mg once-daily for 5 days.
  - The safety parameters evaluated include AEs, clinical laboratory tests, vital signs, physical examinations, and 12 lead ECGs. PK assessments were collected pre-dose and at scheduled time points post-dose on Day 1 to Day 5

Results

MYMD-1® pharmacology in vitro and in vivo

- MYMD-1® has shown selective inhibition of TNFα production by lymphocytes versus Etanercept (**Figure 1a**)
- MYMD-1® inhibited the anti-cluster of differentiation (CD)3/anti-CD28-mediated release of cytokines, including interferon gamma (IFNγ), interleukin (IL)-2, IL-10, and TNFα, from human peripheral blood mononuclear cells (PBMCs) in a dose- dependent manner
- In the murine CAIA model, the therapeutic effect of MYMD-1® on inflammation was assessed by measuring the clinical score and the paw swelling. In addition, at termination, the cytokines levels were analyzed. MYMD-1® at 450 mg/kg/day significantly reduced the clinical score and the paw swelling when compared to the CAIA disease control.
- Results from the mouse CAIA model show percent change of inflammation relative to control was reduced by 37% with MYMD-1® while the reduction was 29% with Etanercept at 10 mg/kg (**Figure 1b**)

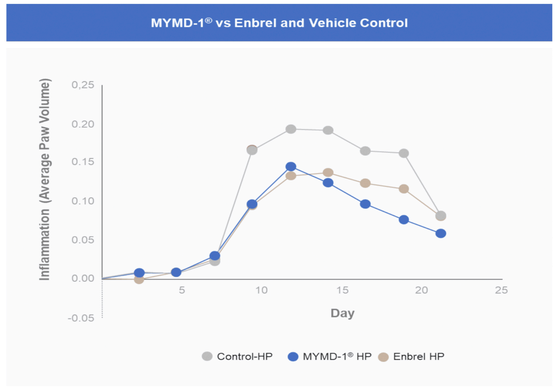
MYMD-1® clinical phase 1 SAD and MAD studies in healthy normal adults

- Single oral doses each of 150 mg, 300 mg, and 450 mg and multiple daily doses of 600 mg were safe and well tolerated in healthy adult subjects.
- Systemic exposures to MYMD-1® were proportional to dose across the dose range of 300 mg to 600 mg when administered as a single dose (**Figure 1c)**. There was minimal accumulation of MYMD-1® following 5 days of once daily dosing at 600 mg. Elimination half-life estimates ranged from approximately 15 minutes to 45 minutes across all doses in the single and multiple dose phases (**Table 2).**

Table 1. Collagen Antibody-Induced Rheumatoid Arthritis (CAIA) Efficacy Model In The Mouse – Study Design

Group	Group Treatment	Arthritis Induction		Test Items			N
		ArthritoMab (mL)	LPS (mL)	Dose level (mg/kg)	Dose Volume (mL/kg)	Route/ Frequency/ Duration	
1	CAIA/ Vehicle	0.2	0.1	0	10	PO/ BID Day 8 to 21	10
2	CAIA/ MyMD1 low dose	0.2	0.1	50	10	PO/ BID Day 8 to 21	10
3	CAIA/ MyMD1 Mid dose	0.2	0.1	250	10	PO/ BID Day 8 to 21	10
4	CAIA/ MyMD1 High dose	0.2	0.1	500	10	PO/ BID Day 8 to 21	10
5	CAIA/ Etanercept	0.2	0.1	10	10	SC/ Every 3 days (Day 8 to 20)	10
6	CAIA/ Dexamethasone	0.2	0.1	0.3	10	PO/ QD Day 8 to 21	5

Figure 1b. MYMD-1® Activity in the CAIA mouse arthritis model demonstrates significant improvements in inhibiting arthritis development



Data are mean from n= 10 per group

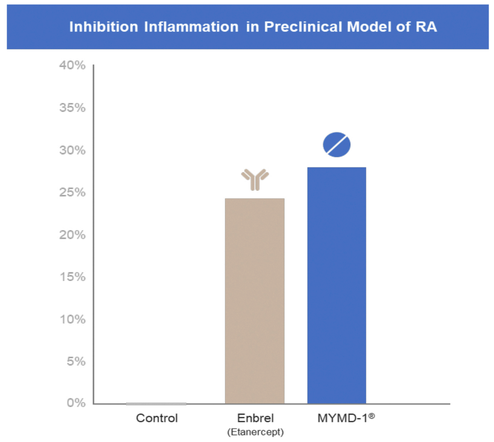
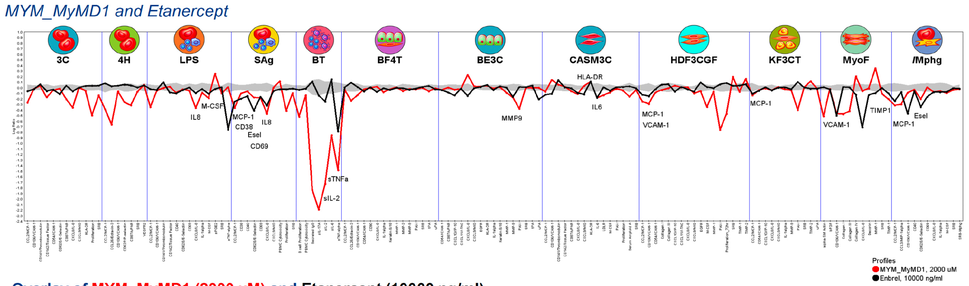


Figure 1a. MYMD-1® and Etanercept



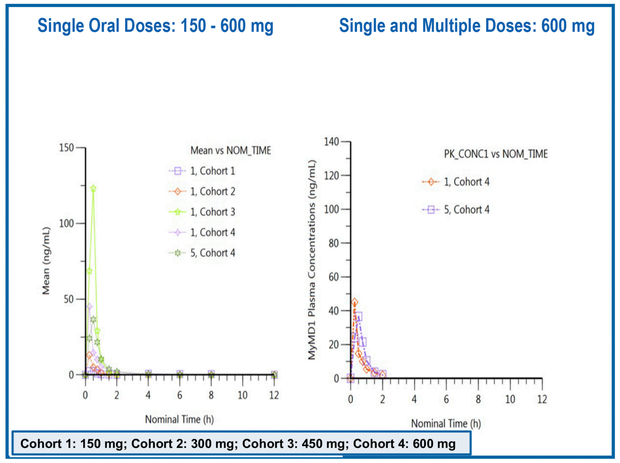
Overlay of MYM_MyMD1 (2000 μM) and Etanercept (10000 ng/ml)

- Etanercept (Enbrel®) is a TNF antagonist used as a treatment for moderate to severe plaque psoriasis, rheumatoid arthritis, and psoriatic arthritis.

MYMD-1® clinical phase 1 SAD and MAD studies in healthy adult subjects

- A total of 32 subjects were enrolled in this study. A total of 4 subjects received a single dose in the "single ascending dose" part of the study and a total of 8 subjects will received multiple doses in the "multiple ascending dose" part of the study.
- Over the single MYMD-1® dose range of 150 mg to 600 mg (4-fold increase in dose) across both the SAD and MAD portions of the study, geometric mean $AUC_{0\text{-last}}$ and C_{max} values increased approximately 3-fold and 9-fold, respectively.
- MYMD-1® elimination half-life following a single dose in both the SAD and MAD portions of the study ranged from approximately 15 minutes to 45 minutes following doses ranging from 300 mg to 600 mg.
- The increase in MYMD-1® exposure was proportional to dose across the dose range of 300 mg to 600 mg when administered as a single dose.
- MYMD-1® single doses each of 150 mg, 300 mg, and 450 mg and multiple doses of 600 mg were safe and well tolerated. No severe AEs, SAEs, or deaths were reported during the study.

Figure 1c. Mean MYMD-1® Plasma Concentration-Time Profiles Following Single 150 mg, 300 mg, 450 mg and 600 mg Oral Doses or Multiple 600 mg doses of MYMD-1®



Cohort 1: 150 mg; Cohort 2: 300 mg; Cohort 3: 450 mg; Cohort 4: 600 mg

Table 2. MYMD-1® plasma pharmacokinetic parameters after administration of a single and multiple oral doses to healthy adult subjects

	Dose of MYMD-1®				
	Single Dose (Day 1)				Multiple Dose (Day 5)
Parameter	150 mg (n = 6)	300 mg (n = 6)	450 mg (n = 6)	600 mg (n = 6)	600 mg (n = 6)
Plasma					
$AUC_{0\text{-last}}$, ng·h/mL	1.516 (0.1440)	5.905 (0.9916)	55.07 (110.7)	20.41 (20.11)	28.03 (12.45)
AUC_{all}, ng·h/mL	1.724 (0.1658)	6.205 (1.003)	55.60 (111.0)	22.22 (20.16)	29.84 (12.85)
C_{max}, ng/mL	3.173 (1.318)	13.961 (4.746)	129.568 (270.977)	46.774 (63.927)	37.778 (26.718)
T_{max}, h	0.25 (0.5, 1.0)	0.25 (0.25, 0.5)	0.25 (0.25, 0.5)	0.25 (0.25, 0.5)	0.5 (0.25, 0.5)
$t_{1/2}$, h	nc	0.4517 (0.2841)	0.2394 (0.0835)	0.8356 (0.4105)	0.8141 (0.5533)
CL/F, L/h	nc	47,000 (6,757)	44,530 (45,590)	37,030 (21,600)	24,060 (11,260)
V_d/F, L	nc	32,010 (23,660)	18,180 (21,360)	52,850 (48,320)	23,610 (13,060)

$AUC_{0\text{-t}}$ = area under the plasma concentration-time curve from time 0 to time of the last quantifiable sample; AUC_{all} = area under the plasma concentration-time curve from time 0 to last sampling timepoint; CL/F = apparent oral clearance; C_{max} = maximum observed plasma concentration; T_{max} = time to reach C_{max}; $t_{1/2}$ = terminal elimination half-life; V_d/F = apparent volume of distribution.nc: not calculated

*All values are mean (SD), except for T_{max} values, which are median (minimum, maximum).

Conclusions

- MYMD1® is an oral, small molecule that can penetrate all parts of the body, including the brain
- In vivo pharmacology profiling of MYMD-1® in a model mimicking rheumatoid arthritis show percent change of inflammation relative to control was reduced by 37% with MYMD-1® while the reduction was 29% with Etanercept.
- In single and multiple dose clinical studies with MYMD-1® at daily oral doses up to 600 mg QD were safe and well tolerated in healthy adult subjects.
- In vitro and in vivo research together with early clinical studies with MYMD-1® support the continued clinical development for various autoimmune diseases.

Author Disclosures

Jenna Brager, Adam Kaplin, and Chris Chapman are employees of MyMD Pharmaceuticals, Inc. Ronald Christopher is an independent consultant.

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