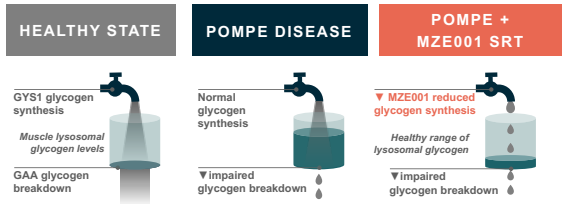
# Results from a first in human study of MZE001, an orally bioavailable inhibitor of glycogen synthase 1 and potential substrate reduction therapy for Pompe Disease

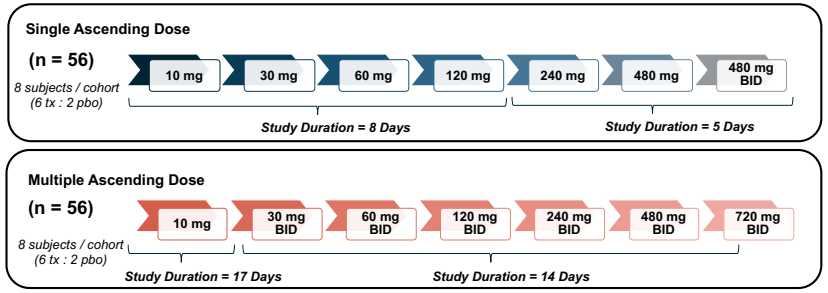
Julie C. Ullman, Todd Minga, Bernard Chung, Janet M. Leeds, Tonya Marmon, Daniela Linzner, Ryan A. Dick, Marie Kim, Terrence F. Satterfield, Oscar Alcantar, Belinda DeLeon, Sanjay J. Chandriani, Joel M. Neutel, Sarah B. Noonberg, Eric M. Green, Harold S. Bernstein *Maze Therapeutics, South San Francisco, CA*

## Introduction

Substrate reduction therapy (SRT) has been proposed as a novel mechanism to treat patients with Pompe disease. We previously reported the discovery of an orally bioavailable small molecule inhibitor of GYS1, MZE001, that reduces glycogen in Pompe model mice. Here, we present results from the first in human single and multiple ascending dose study of MZE001 in healthy volunteers. In 112 participants, MZE001 was well-tolerated up to a single dose of 480 mg BID and multiple doses of 720 mg BID for ten days. At higher dose levels, MZE001 achieved plasma levels in a range that reduced muscle glycogen levels in preclinical models of Pompe disease. The half-life of MZE001 in plasma was ~12 hours, compatible with twice daily oral dosing. We also measured glycogen in PBMCs, which correlates with muscle glycogen levels in preclinical models. Treatment with MZE001 for ten days reduced PBMC glycogen in a dose-dependent manner. Taken together with our preclinical studies, these data support advancing to Phase 2 studies in patients with Pompe disease.



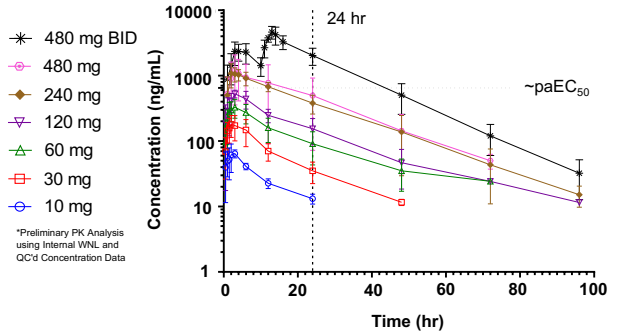

## MZE001 Single Ascending Dose (SAD) & Multiple Ascending Dose (MAD) in Healthy Volunteers

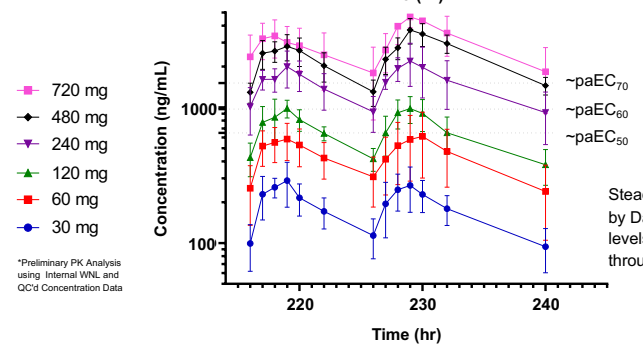



## MZE001 was well-tolerated in the First-in-Human study in healthy volunteers

- Well-tolerated at single doses up to 480mg and multiple doses up to 720mg BID for 10 days
- Few Treatment Emergent Adverse Events observed
  - 25 of 27 mild, 2 moderate
- No abnormal laboratory trends
- No clinically relevant ECG abnormalities
- No change in exercise tolerance

## MZE001 SAD/MAD Preliminary* Pharmacokinetics

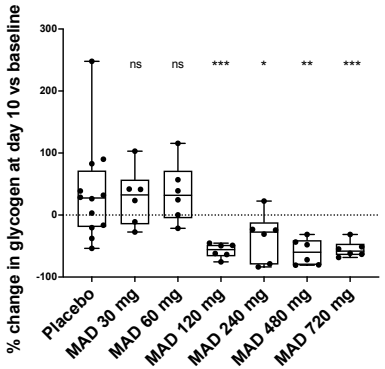


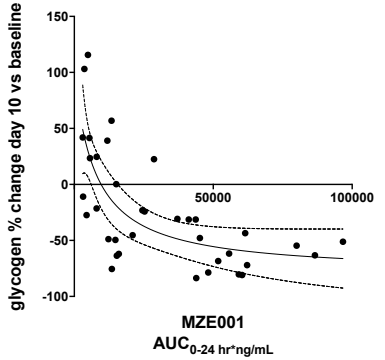

- Approximately dose proportional PK single doses
- Mono-exponential elimination with median $T_{1/2}$ ~12 hours
- PK profile supports twice-daily dosing
- Variability (%CV) for AUC ranges from 14-69%
- No significant food effect

Steady state achieved by Day 5, with trough levels consistent through Day 10

## MZE001 dose dependent reduction in PBMC glycogen confirms GYS1 target engagement




Min-max, median; Ranked ANCOVA vs Placebo ns p>0.05, *p<0.05, **p<0.01, ***p<0.001




3 parameter non-linear curve fit with 95% confidence intervals; R^2 = 0.4997

- Exposure-dependent reduction in PBMC glycogen observed after 10 days with MZE001 120, 240, 480 and 720 mg BID in healthy volunteers.

## MZE001 Phase 1 healthy volunteer data supports initiating clinical PoC study in patients

- Full evaluation of dose-exposure completed
- MZE001 well-tolerated at all doses through 720 mg BID in HVs
- MZE001 exposures achieved 50-75% glycogen reduction in preclinical studies
- MZE001 PBMC glycogen exposure-response supports GYS1 Proof of Mechanism
- Dose selection for Phase 2 / Proof of Concept (PoC) in patients with Pompe Disease underway

❖ **Taken together with preclinical studies, these data support further investigation of MZE001 as a potential first oral therapy for patients with Pompe Disease, either as monotherapy or in combination with ERT**

❖ **Phase 2 clinical PoC study in patients with Pompe Disease to start in 2023**