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

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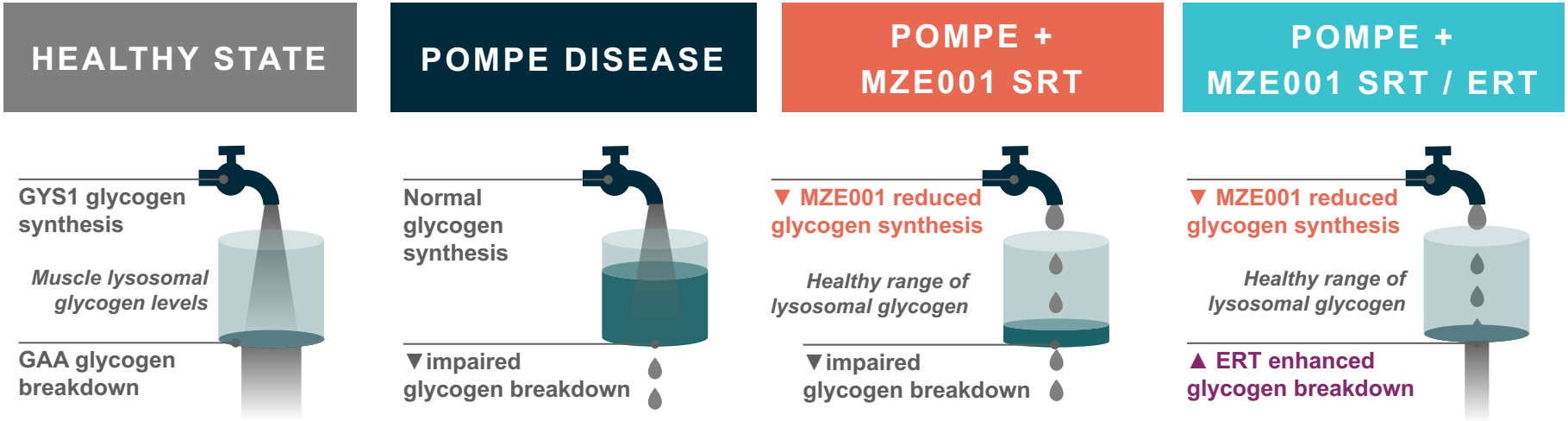
Substrate Reduction Therapy (SRT) for Pompe Disease: *Novel Mechanism of Action*



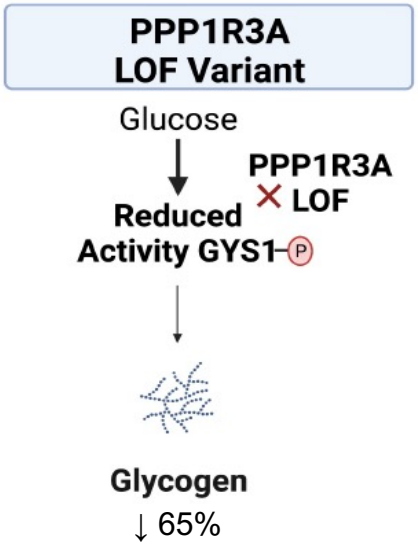
SUBSTRATE REDUCTION THERAPY is a novel approach to reduce glycogen burden by **REDUCING glycogen synthesis.**

MZE001 Preclinical Therapeutic Dose Hypothesis

- UK biobank phenome analysis shows human muscle glycogen reduced by ~paEC$_{60\text{-}80}$ of normal is well tolerated
- MZE001 exposure-dependent reduction in PBMC glycogen in healthy dogs correlates with reduced muscle glycogen and may be a useful human biomarker for dose selection
- Chronic GYS1 inhibitor SRT treatment at ~paEC$_{65}$ +/- ERT reduces muscle glycogen in Pompe mice

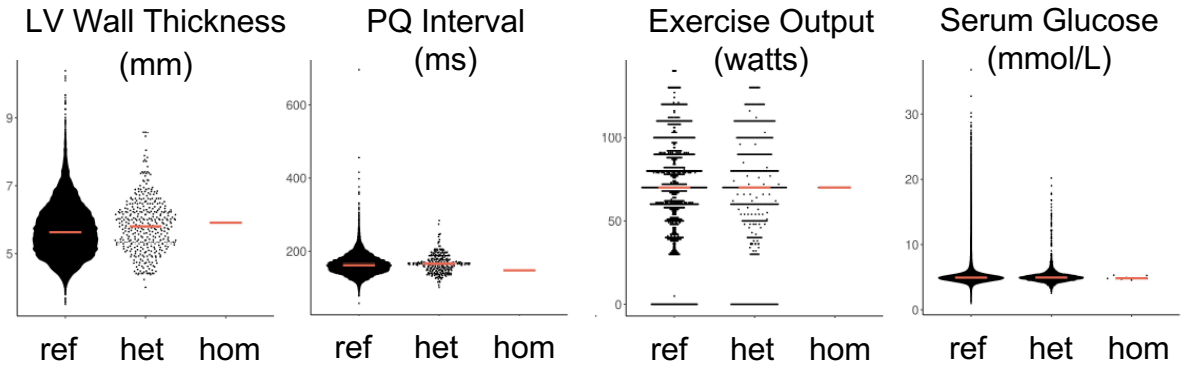
MZE001 doses that achieve ~paEC$_{60\text{-}80}$ may be safe, well tolerated, and efficacious in reducing pathological glycogen stores in patients with late-onset Pompe disease

Reduction of muscle glycogen in humans by ~65% may be well tolerated



(Savage et al PLOS Med 2008)

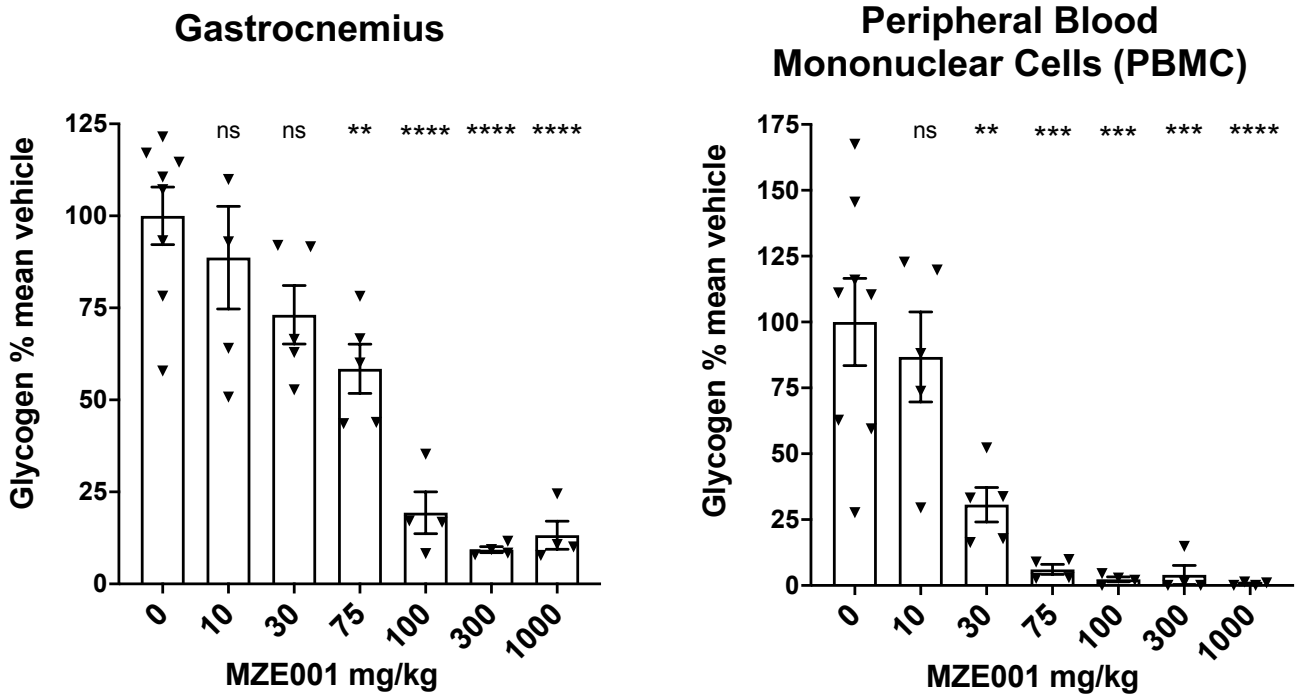
No association between PPP1R3A LOF and quantitative phenotypes in healthy participants in UK Biobank



(Homburger et al WORLD 2022)

Human biobank phenome analyses support the tolerability of chronic reduction in muscle glycogen at levels ~60-80% less than normal stores.

MZE001 dose dependent reduction in dog gastrocnemius glycogen & PBMC glycogen



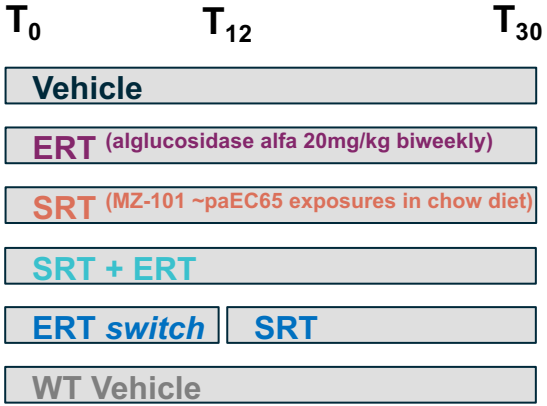
7-day dosing in healthy dogs, Data: mean $\pm SEM$ one-way ANOVA, Dunnett's vs Vehicle 0 mg/kg, ns p>0.05, * p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

MZE001 dose-dependent reduction in dog PBMC glycogen correlates with reduced muscle glycogen, and may be a useful human biomarker for dose selection.

Preclinical studies support therapeutic potential of SRT in Pompe disease

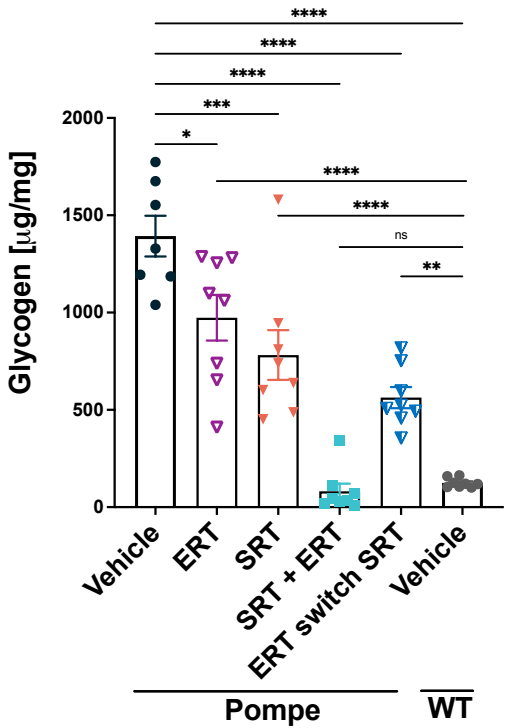
Study design

Male Mice 6-9 wks old at intervention start
Treatment time (T) in weeks



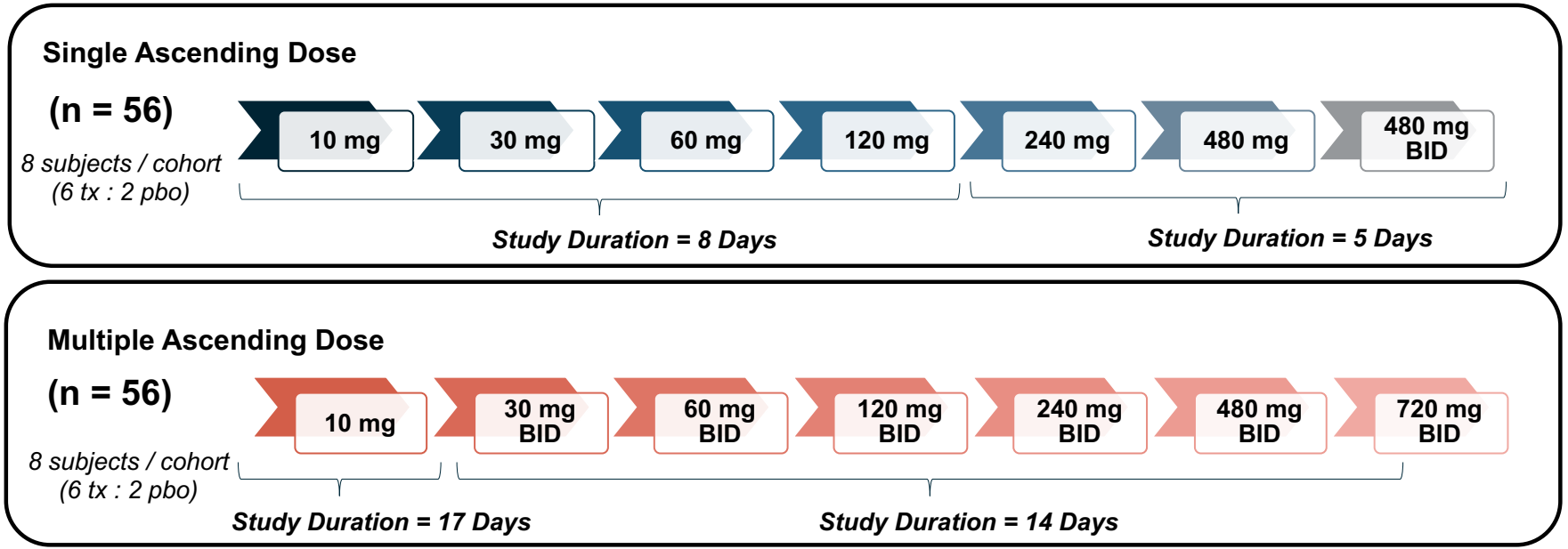
Data: mean +/-SE, One-way ANOVA with Tukey's post-hoc NS p>0.05, * p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Gastrocnemius



Pompe mouse data demonstrates potential impact of ~paEC$_{65}$ SRT as a monotherapy, combination therapy with ERT, and switch therapy post ERT.

MZE001-01 Single Ascending Dose (SAD) & Multiple Ascending Dose (MAD) in Healthy Volunteers



Primary Objective: safety & tolerability

Secondary Objective: PK

Exploratory Objective: urine and blood biomarkers of glycogen metabolism

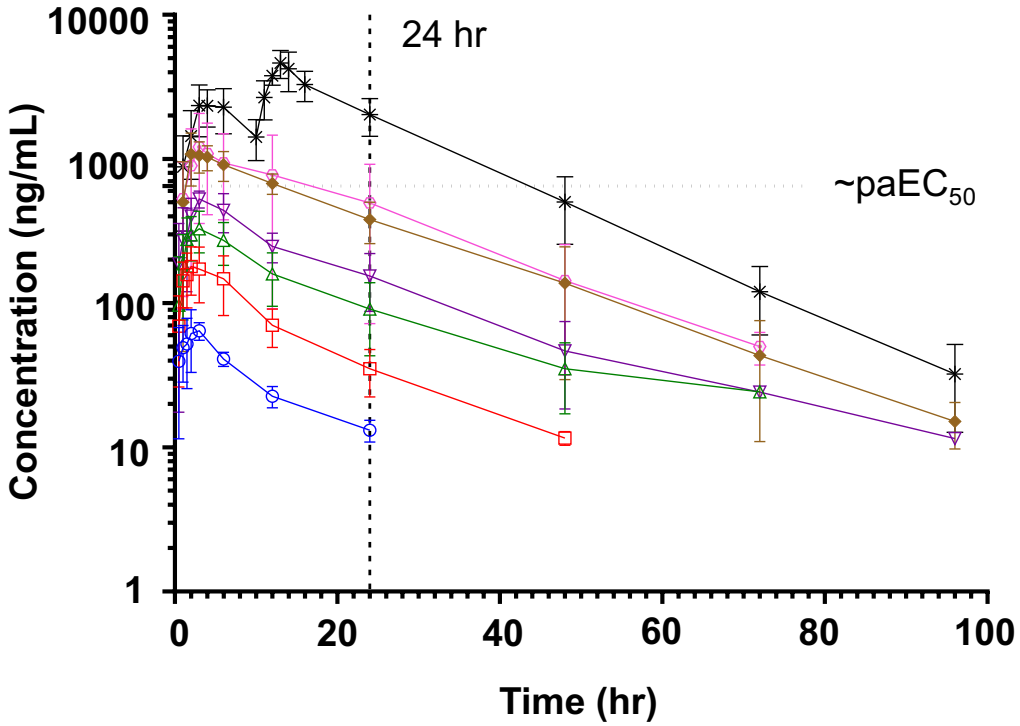
MZE001 was well-tolerated in the First-in-Human study in healthy volunteers

- 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
  - 5 were related to study drug; 4 of these 5 were ultimately deemed to be result of a lab error
- No abnormal laboratory trends
- No ECG abnormalities
- No change in exercise tolerance

MZE001-01 SAD Pharmacokinetics Preliminary Data*

480 mg BID
480 mg
240 mg
120 mg
60 mg
30 mg
10 mg

*Preliminary PK Analysis using Internal WNL and QC'd Concentration Data

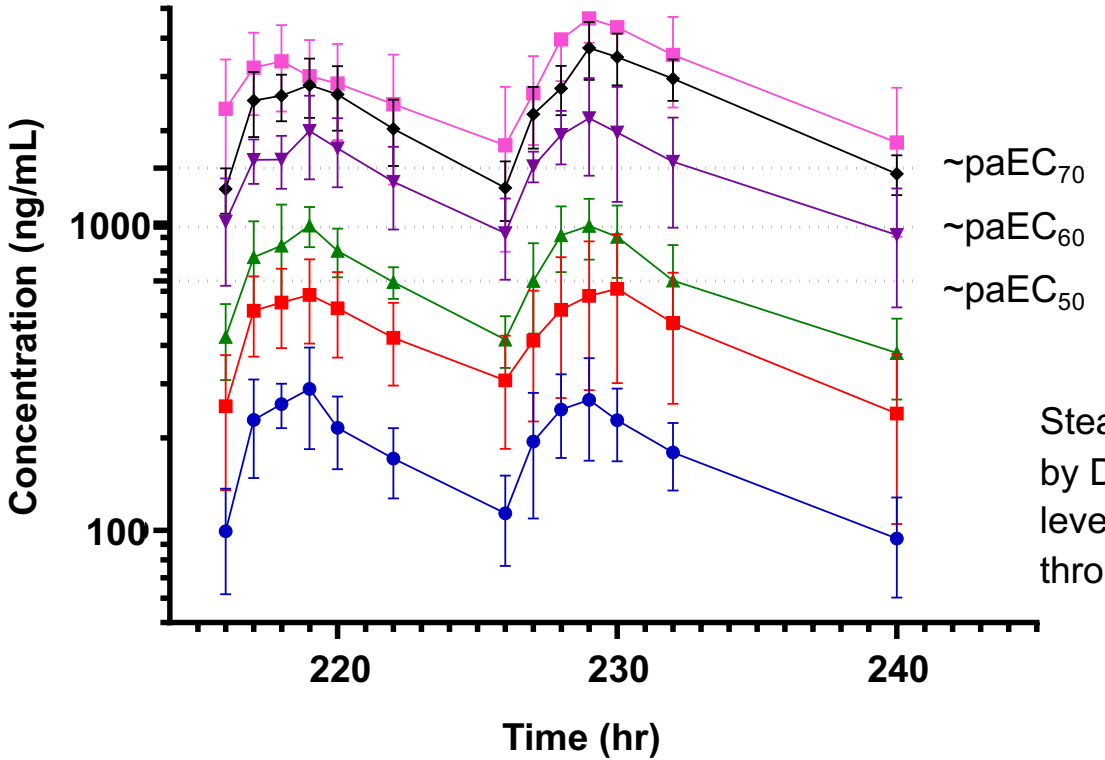


- Approximately dose proportional PK single doses
- Mono-exponential elimination with median $T_{1/2}$ ~12 hours
- PK profile supports twice-daily dosing
- Variability (%CV) for AUC ranges from 14-69%
- No significant food effect

MZE001-01 MAD Pharmacokinetics Day 10 Preliminary Data*

720 mg
480 mg
240 mg
120 mg
60 mg
30 mg

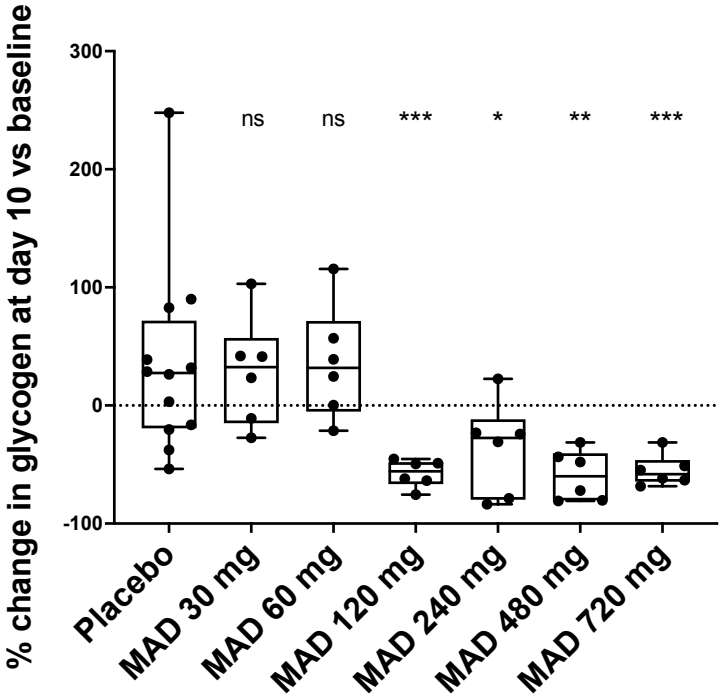
*Preliminary PK Analysis using Internal WNL and QC'd Concentration Data



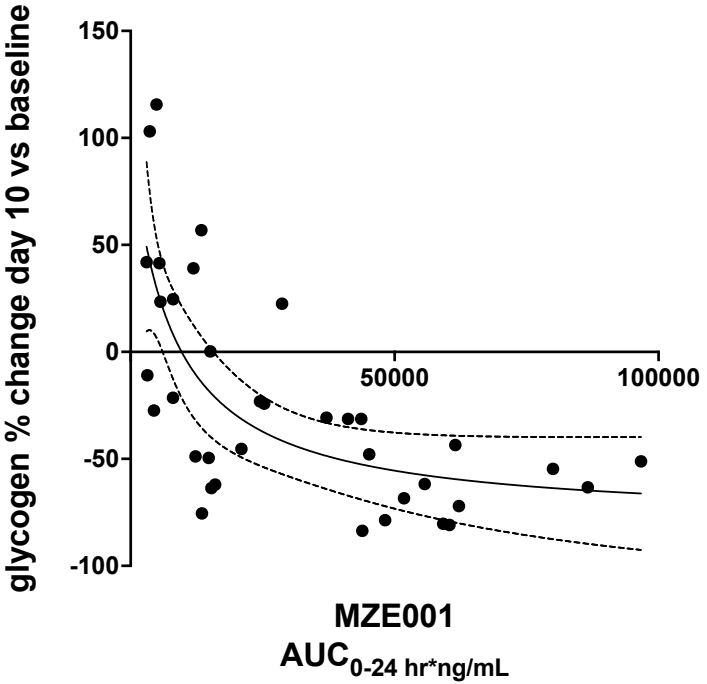
Steady state achieved by Day 5, with trough levels consistent through Day 10

Doses of 240, 480 and 720 mg BID exceed $paEC_{50}$, $paEC_{60}$, and $paEC_{70}$ at trough, respectively.

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



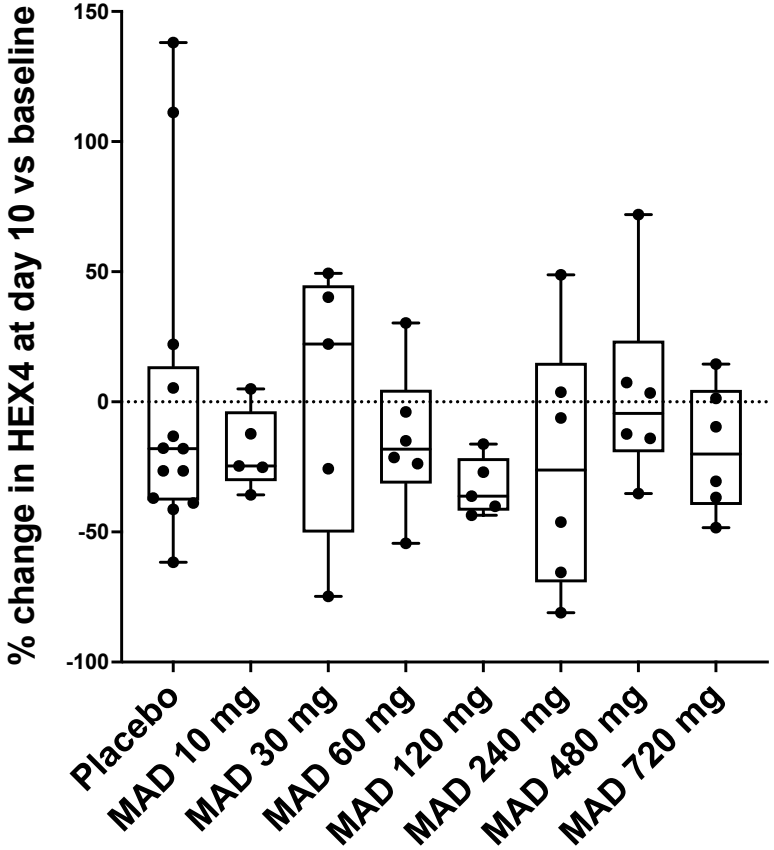
Min-max, median; Ranked ANCOVA vs Placebo ns p>0.05, *p<0.05, **p<0.01, ***p<0.001



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.

HEX4 (uGlc4) does not change with MZE001 dose in healthy volunteers



Min max median, Rout analysis 4 outliers removed

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 for its potential to be the 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**

Acknowledgements

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Human genetics research has been conducted using data from UK Biobank, a major biomedical database.

For more information please see:

POSTER #321 "Quantification of peripheral blood mononuclear cell (PBMC) glycogen as a novel biomarker for therapeutic intervention in Pompe Disease "

POSTER #355 "Small molecule inhibition of glycogen synthase 1 restores autophagolysosomal and metabolic pathway dysfunction in a mouse model of Pompe disease"

POSTER #LB-65 "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"