



Maze Therapeutics Presents New Preclinical Data Supporting Advancement of MZE001 as a Potential Treatment for Pompe Disease

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Findings Highlight Potential of Oral Substrate Reduction Therapy to Lower Disease-Causing Glycogen Build-up as a Treatment for Pompe Disease

Data Support Advancement of MZE001 into Phase 1 Clinical Trial Expected to Start in First Half of 2022

SOUTH SAN FRANCISCO, CA., Feb. 10, 2022– Maze Therapeutics, a company translating genetic insights into new precision medicines, today announced new preclinical data supporting the advancement of MZE001, which aims to address Pompe disease by reducing pathologic glycogen accumulation through the inhibition of muscle glycogen synthase (GYS1). Data are being [presented during](#) two oral presentations and two poster sessions at the 18th Annual WORLD Symposium being held February 7-11, 2022.

Pompe disease is a rare, inherited disorder caused by mutations in the gene coding for acid alpha-glucosidase (GAA), an enzyme responsible for degrading lysosomal glycogen into glucose monomers. These mutations lead to the buildup of lysosomal glycogen, primarily in skeletal muscle, respiratory muscle and cardiac muscle tissues, leading to progressive weakness and respiratory compromise.

In several *in vitro* and *in vivo* analyses with GYS1 inhibitors presented and highlighted below, data demonstrated potent inhibition of GYS1, leading to reduced accumulation of glycogen through a substrate reduction approach. Importantly, GYS1 inhibition was generally well-tolerated with no on-target or off-target toxicity observed.

“Pompe disease affects both people who are living with the disease, as well as their caregivers. Whilst enzyme replacement therapy has been lifesaving, disease progression, including skeletal muscle and respiratory muscle weakness still occurs in some patients,” said Priya Sunil Kishnani, M.D., Duke Department of Pediatrics, Duke University Medical School. “I am encouraged by the preclinical data from Maze’s program targeting glycogen synthesis, which could potentially offer a new and complementary treatment option for these patients.”

“These data are the first to be presented from a program that has emerged from our proprietary Compass platform, providing validation for our approach focused on translating genetic insights from disease-associated pathways to design and develop novel therapeutics,” said Sarah Noonberg, M.D., Ph.D., chief medical officer of Maze. “This work demonstrates the potential value of our substrate reduction approach across the Pompe disease spectrum both as combination therapy and as monotherapy. We are excited to continue our efforts with this program as we advance MZE001 toward the clinic.”

Taken together, the preclinical data support the potential for a GYS1 inhibitor, such as MZE001, as a treatment for Pompe disease. Based on these findings, Maze is advancing MZE001 toward clinical development, with plans to initiate a Phase 1 clinical trial in healthy volunteers in the first half of 2022.

Detailed findings from each of the presentations are as follows:

Title: *In vitro* characterization of MZE001, an orally active GYS1 inhibitor to treat Pompe disease

Data Summary: In *in vitro* assays, treatment with MZE001 demonstrated:

- Potent inhibition of glycogen synthesis in several human and animal *in vitro* assays, including in cells from healthy volunteers and patients with Pompe disease, as well as wild-type and disease model rodent tissue
- A high degree of selectivity for GYS1 over the closely related liver isoform GYS2, as well as other off target effects

Title: Substrate reduction therapy for Pompe disease: small molecule inhibition of glycogen synthase 1 in preclinical models

Data Summary: In *in vivo* models, treatment with GYS1 inhibitors demonstrated:

- Dose dependent inhibition of glycogen synthesis with no effect on glycogen synthesis in the liver
- Reduced accumulation of glycogen as measured directly in tissues and by circulating biomarkers in multiple species
- Lower muscle glycogen and improved cellular markers of muscle pathology, including lysosomal function and autophagy
- Augmented glycogen reduction in skeletal muscle when combined with standard of care enzyme replacement therapy

- GYS1 inhibition was generally well tolerated across the studies

Title: #327. Pharmacology of small molecule inhibitors of GYS1 in canines and a mouse model of Pompe disease

Data Summary: In *in vivomouse* and canine models, inhibition of GYS1 demonstrated:

- Potent and specific inhibition of GYS1
- Reduced tissue glycogen following treatment with MZE001 in a canine model, which strongly correlates with decreased biomarkers
- Reduced elevated glycogen levels in skeletal muscle following chronic treatment with MZ-101, a MZE001 precursor, in a mouse model, which is associated with improvements in markers of cellular dysfunction
- Combination therapy of MZ-101 and enzyme replacement therapy normalized tissue glycogen and restored cellular homeostasis

Title: #122. Genetic reduction of muscle glycogen is well tolerated in UK Biobank participants

Data Summary: Analyses of individuals in the UK Biobank with reduced muscle glycogen levels due to variants in PPP1R3A, a regulator of glycogen metabolism, showed:

- No impact of partial reduction of muscle glycogen on any evaluated health outcomes or quantitative measures of cardiac structure or function, exercise capacity or circulating glucose
- Lifelong partial reduction of muscle glycogen levels is well tolerated

About Maze Therapeutics

Maze Therapeutics is a biopharmaceutical company applying advanced data science methods in tandem with a robust suite of research and development capabilities to advance a pipeline of novel precision medicines for patients with genetically defined diseases. Maze has developed the Maze Compass™ platform, a proprietary, purpose-built platform that combines human genetic data, functional genomic tools and data science technology to map novel connections between known genes and their influence on susceptibility, timing of onset and rate of disease progression. Using Compass, Maze is building a broad portfolio of wholly owned and partnered programs. Maze is based in South San Francisco. For more information, please visit mazetx.com, or follow us on [LinkedIn](#) and [Twitter](#).

Contacts:

Jillian Connell, Maze Therapeutics

jconnell@mazetx.com

650.850.5080

Media:

Katie Engleman, 1AB

katie@1abmedia.com