



# Expanding therapeutic options for Pompe disease: a new small molecule inhibitor of glycogen synthase 1 (GYS1) shows preclinical promise in Pompe disease

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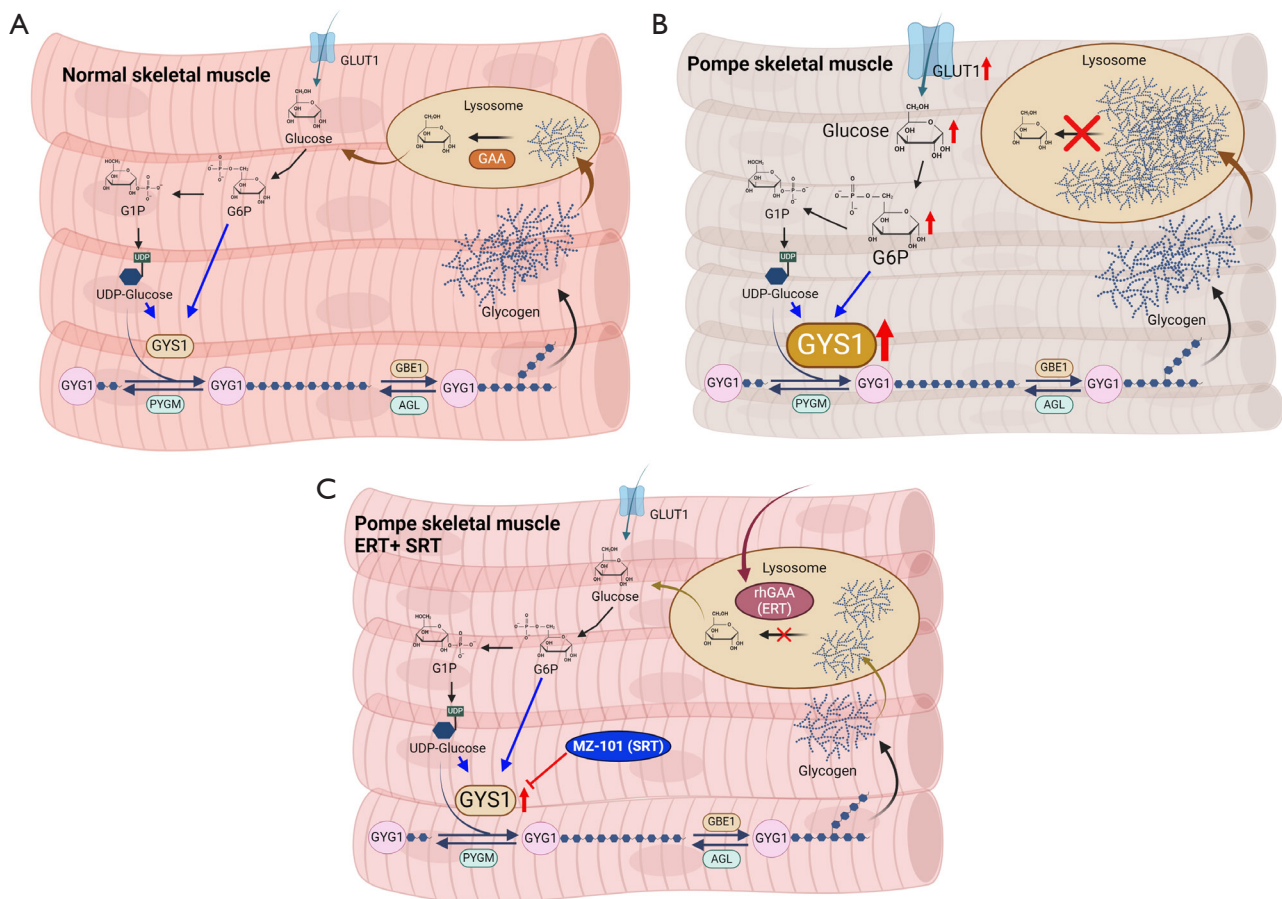
Pompe disease, also called glycogen storage disease (GSD) type II, is a severe neuromuscular disorder caused by biallelic loss-of-function (LOF) variants in the *GAA* gene. *GAA* encodes a lysosomal enzyme acid  $\alpha$ -glucosidase (GAA), which is responsible for breaking down glycogen to glucose within lysosomes. GAA deficiency leads to lysosomal glycogen accumulation, dysregulation of autophagy, and downstream effects, including mitochondrial dysfunction.

The phenotypic spectrum of Pompe disease includes infantile-onset and late-onset Pompe disease (IOPD and LOPD, respectively) based on the levels of residual endogenous GAA activity and the presence/absence of cardiomyopathy in the first year of life. IOPD manifests as severe early cardiomyopathy, while LOPD can present at any age and had been previously categorized as juvenile-, childhood-, and adult-onset forms. The natural progression of the disease in untreated IOPD patients leads to death in infancy or early childhood due to cardiorespiratory failure. The approval of human recombinant GAA (rhGAA;  $\alpha$ -glucosidase alfa) enzyme replacement therapy (ERT) in 2006 changed the course of Pompe disease, leading

to improved survival and reversal of cardiomyopathy in IOPD as well as improvement or stabilization of motor and pulmonary outcomes in LOPD.

With the inclusion of Pompe disease in the newborn screening panel in most US states and many other countries, patients are detected earlier and clinical outcomes have greatly improved (1,2). Treatment as early as during fetal development has shown great promise (3). Yet, with patients living longer, a new natural history of ERT-treated Pompe disease is emerging, and the limitations of ERT are well recognized. Notably, poor biodistribution and inefficient rhGAA uptake by skeletal muscle cells result in inadequate clearance of glycogen in this tissue. In addition, residual glycogen accumulation is also noted in cardiac tissues despite improvements in cardiomyopathy and cardiac function. To address the limitations of  $\alpha$ -glucosidase alfa, next-generation ERTs— $\alpha$ -glucosidase alfa and cipaglucosidase alfa with miglustat—have been developed with improved targeting to skeletal muscle. These treatments have been approved for use in LOPD and some countries have approved the use of  $\alpha$ -glucosidase

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**Figure 1** Overview of SRT and ERT in Pompe disease skeletal muscle. (A) In healthy skeletal muscle, glucose enters the muscle fiber through the GLUT1, and it is converted to G6P, G1P, and UDP-glucose. G6P is an allosteric activator of GYS1. UDP-glucose binds first to GYG1 which forms a complex with GYS1. This leads to an elongated linear polymer of glucose that is branched by GBE1 to form soluble, branched glycogen. Glycogen is broken down in the cytosol by the actions of glycogen phosphorylase (myophosphorylase; PYGM) and debranching enzyme (AGL), as well as in the lysosome by GAA. (B) In Pompe disease, loss of GAA leads to glycogen accumulation in the lysosome. An increase in GLUT1 leads to increased G6P and free glucose in the cytosol. G6P activates GYS1, which further worsens the lysosomal storage of glycogen. (C) ERT delivers the rhGAA to the lysosomes. SRT with MZ-101 inhibits GYS1 activity, reducing the amount of glycogen produced in skeletal muscle. Created with BioRender.com. GLUT1, glucose transporter 1; G1P, glucose-1-phosphate; G6P, glucose-6-phosphate; UDP, uridine diphosphate; GYS1, glycogen synthase 1; GYG1, glycogenin 1; GBE1, glycogen branching enzyme 1; GAA, acid  $\alpha$ -glucosidase; rhGAA, human recombinant GAA; SRT, substrate reduction therapy; ERT, enzyme replacement therapy.

alfa for IOPD. There are ongoing clinical trials designed to better understand how these next-generation ERTs benefit patients (NCT02675465; NCT03911505; NCT04910776) compared to standard of care  $\alpha$ -glucosidase alfa. Despite these advancements, including an increased dose of ERT and the use of immune tolerance induction (ITI) to prevent antidrug antibodies, challenges remain. These hurdles include infusion-associated reactions, breaking tolerance, incomplete muscle glycogen clearance, and the burden on quality of life for both the patient and the caregiver

given the high frequency and duration of the infusions. Therefore, there is an urgent need for additional treatment options for patients with Pompe disease.

Rather than replacing the defective enzyme, alternative approaches have been proposed, including substrate reduction therapy (SRT)—a strategy that involves targeting the glycogen synthesis pathway directly to reduce glycogen production and, thus, accumulation in cells (Figure 1). A logical target would be glycogen synthase (GYS) which is a rate-limiting enzyme for glycogen synthesis and is

responsible for creating the linear glycosidic bonds in glycogen. There are two isoforms of GYS in mammals: (I) GYS1, which is highly expressed in muscle cells as well as in most other tissues, and (II) GYS2, which is highly and specifically expressed in the liver. Several groups have recently published high-resolution structures of the human GYS1 tetramer in complex with portions of glycogenin (4-6). These studies uncovered the structural logic and the mechanism of GYS1 regulation, including (I) allosteric activation by glucose-6-phosphate (G6P) binding and (II) inhibition by phosphorylation of numerous residues at the amino (N)- and carboxyl (C)-terminal sites that are sensed by distinct arginine clusters (6). Several approaches to therapeutically reduce GYS1 activity in Pompe muscles have been proposed, including small-molecule inhibition, antisense oligonucleotide (ASO), and RNA interference (RNAi) (7-9).

Ullman and colleagues recently published *in vivo* efficacy data supporting the use of a selective GYS1 oral small molecule inhibitor to reduce glycogen burden and ameliorate muscle cell pathology in Pompe disease (10). The authors performed a high-throughput screen of small molecules using purified phosphorylated GYS1 (GYS1-p) in the presence of a physiological concentration of G6P (0.5 mM). This provided a balance between inhibiting phosphorylation and G6P-mediated activation, potentially mimicking an intermediate state of GYS1 cellular activity. The goal of the screen was to identify compounds that (I) inhibit the activity of GYS1 (the isoform expressed in muscle) but (II) do not impact the activity of GYS2 (the isoform expressed in the liver). The initial screen identified MZ-101, the compound which was extensively studied for the remainder of the article. Unfortunately, the authors did not indicate if this compound was one of several identified hits or how it was selected; limited information is given about the library of small molecules used or the diversity of compounds screened.

Following the initial screen, the researchers evaluated the inhibitory potency of MZ-101 using a range of physiologically relevant concentrations of G6P and uridine diphosphate (UDP)-glucose (the sugar donor) and both phosphorylated (inactive) and dephosphorylated (active) GYS1. Increasing concentrations of both G6P and UDP-glucose led to an increase in half-maximal inhibitory concentration of MZ-101; this was true in the presence of phosphorylated GYS1 and fully dephosphorylated GYS1 suggesting a noncompetitive mechanism of MZ-101 inhibition. The most likely explanation for these findings

is that MZ-101 acts as a negative allosteric modulator of GYS1 which binds to a site on the protein that is distinct from the binding sites for UDP-glucose or G6P. Future structural studies to identify the binding site of MZ-101 on GYS1 may provide further mechanistic understanding.

Having identified MZ-101—a small molecule inhibitor of GYS1 with no impact on the function of GYS2—the authors proceeded to test the drug in human cells. Primary fibroblast cultures were obtained from three healthy individuals and three individuals with IOPD. IOPD fibroblasts stored 1.5 to 2 times more glycogen than healthy cells; upon MZ-101 treatment, glycogen reduction was observed in both healthy and IOPD-derived fibroblasts, although the levels remained elevated in the diseased cells. The team then turned to a well-described Pompe knockout mouse model (KO) for further investigations (11). They first studied the protein level, activity, and phosphorylation state of GYS1 in KO skeletal muscle. The findings can be summarized as follows: increased GYS1 phosphorylation and activity with no changes in the total protein levels. The counterintuitive increase in GYS1 activity (~2 fold) in the context of increased phosphorylation is attributed to the allosteric activation by G6P, which was shown to be elevated in the Pompe muscle. The increased GYS1 activity was confirmed by functional assay and consistent with the results by others (12).

Next, a clever metabolic tracer array assay was employed to measure *de novo* glycogen synthesis *in vivo* in muscle tissue of KO mice. By feeding mice for a short period with stable isotope-labeled  $^{13}\text{C}_6$ -glucose, Ullman and colleagues demonstrated that glycogen synthesis was increased in muscle of KO mice as indicated by the increased (~2 fold) incorporation of  $^{13}\text{C}_6$ -glucose into glycogen. Once again, these data are consistent with the elevated GYS1 activity in the diseased muscle. This ability to measure glycogen synthesis *in vivo* allowed the researchers to quantify the extent of GYS1 inhibition by MZ-101: the compound significantly reduced  $^{13}\text{C}_6$ -glucose incorporation in both WT and KO muscle but not in the liver, where GYS2 is predominantly expressed. The researchers rightly point out that in order to ensure a meaningful reduction in glycogen accumulation by SRT, “the rate of glycogen catabolism must exceed the rate of glycogen synthesis”. Therefore, the authors measured glycogen turnover in the muscle by incorporating the metabolic tracer assay (with a bolus of  $^{13}\text{C}_6$ -glucose) into a pulse-chase experiment to track the reduction in labeled glucose; the turnover was ~16 hours in WT muscle, whereas the process was much slower and

took weeks in KO muscle. This is a novel and intriguing finding. These results also provided a rationale for the duration of MZ-101 treatment required to reduce glycogen levels in KO skeletal muscle. Consequently, MZ-101 was administered to KO mice for 4 to 14 weeks, leading to a reduction (up to 58% by 14 weeks) of muscle glycogen load. However, glycogen levels were still higher than those in WT muscles, suggesting that a combination of MZ-101 with ERT may be needed to normalize glycogen in the diseased muscles.

To further assess the impact of MZ-101 on glycogen synthesis and cellular metabolism, young KO mice (6- to 9-week-old animals) were treated for 12 weeks with ERT (alglucosidase alfa), MZ-101, or MZ-101 in a combination with ERT. Multiple parameters including the phosphorylation state of GYS1, glucose transporter 1 (GLUT1) abundance, glycogen content, and levels of glycolytic intermediates (glucose, G6P, lactate, pyruvate, etc.) were analyzed. In our view, the outcome of this series of experiments is somewhat puzzling. ERT alone seemed to have little, if any impact, whereas MZ-101 significantly improved many of these outcome measures. Importantly, glycogen reduction over the 3-month period on ERT at a dose of 20 mg/kg every 2 weeks did not reach statistical significance; this contrasts with multiple studies, including the reports which are cited by the authors in support of their findings (13-15).

Many of the above-mentioned parameters have been previously evaluated in KO muscles and in muscle biopsies from patients with Pompe disease, and there are some discrepancies in the reported data. A significant increase in the amount of total GYS1 in KO muscle was reported in young mice (16-week-old) by Taylor *et al.*, while others observed an increase only in old 60-week-old KO mice (12,16). On the other hand, similar to what was observed by Ullman and colleagues, an increase in phosphorylated GYS1 (pS641, a major site involved in the activity regulation) without changes in the total amount of protein was reported by Xu *et al.* [2019] and Douillard-Guilloux *et al.* [2010] (15,17). Another inconsistency—and perhaps most striking—was the levels of G6P, an allosteric activator of GYS1; Ullman and colleagues reported a significantly elevated level of this metabolite in KO gastrocnemius muscle, whereas Meena *et al.* [2020] observed a decrease in G6P in KO (particularly in older animals) when only the pale part of gastrocnemius muscle was analyzed (18). These findings suggest that the mouse genetic background, sex, age, and difference in types of muscle fibers may play a role.

Notwithstanding the differences, there is a general agreement that the diseased muscles exhibit (I) elevated levels of glucose transporters (10,17-19), (II) increased activity of GYS1 (10,12), and (III) extra-lysosomal glycogen accumulation (10,16,20,21). These data support the notion that muscle glycogen metabolism is profoundly dysregulated in Pompe disease, and that there is a crosstalk between lysosomal glycogen degradation and the well-established cytosolic glycogenolyses.

The safety and efficacy of MZ-101 has not yet been tested in patients with Pompe disease. However, a Phase 1, randomized, double-blind, placebo-controlled study with single and multiple ascending doses was completed in 2022 to evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered MZE001 (MZ-101 compound) in healthy adult subjects in both fasted and fed states (NCT05249621). Unfortunately, published data on the clinical trial is not yet available. Encouraging data on this first-in-human trial of MZE001 was presented at the *WORLD Symposium* in 2023, with the company (Maze Therapeutics) highlighting the ability of MZE001 to selectively inhibit GYS1 and reporting that the drug was well tolerated in the 112 participants with doses up to 720 mg twice daily (22). Based on these results, the company reported that it plans to advance to a Phase 2 trial in patients with Pompe disease.

Here, we would like to emphasize the importance of enrolling both ERT-treated and untreated (naïve) patients into a clinical trial. Symptomatic LOPD patients who cannot access ERT or do not tolerate the therapy may be appropriate candidates for the latter cohort. In addition, in light of the emerging early-onset phenotype in LOPD, these patients can be potentially eligible for MZE001 treatment. Careful selection of participants will be critical. The impact of a LOF variant in *GYS1* and *PPP1R3A* (a key activator of GYS1 that dephosphorylates it) will be essential to evaluate. As highlighted by Savage and colleagues, individuals heterozygous for a predicted protein truncating variant in *PPP1R3A* (referred to as *PPP1R3A FS*) exhibit a ~65% reduction in muscle glycogen levels (23). Ullman and colleagues conducted a phenome-wide association study involving the *PPP1R3A FS* variant, encompassing 3561 heterozygous carriers and 9 biallelic homozygous carriers; no statistically significant associations were found with any disease diagnosis, ICD10 code, fluid biomarker, or measures of heart structure or function, suggesting that long-term glycogen reduction by ~65% could be well tolerated in humans. The authors also noted that pharmacologic

inhibition through MZ-101 is different from lifelong impact of genetic variants in *PPP1R3A* or *GYS1*, emphasizing the necessity of clinical studies to delineate the therapeutic window for *GYS1* SRT in human applications.

At this time, it is unclear to what level *GYS1* activity can be reduced without negative effects. *GYS1* LOF variants appear to be rare in the general population. In the recently released and updated gnomAD v4.1, 692 predicted *GYS1* LOF alleles are reported across approximately 160,000 sequenced alleles for an allele frequency of 0.0004. Though rare in the general population, we would encourage screening patients for *GYS1* LOF variants prior to initiating treatment with a *GYS1* inhibitor. Complete or near complete loss of *GYS1* activity, as seen in patients with biallelic LOF variants in *GYS1* (GSD type 0b), can lead to muscle weakness and fatal cardiac arrhythmias (24,25).

Assessing the effect of *GYS1* reduction by MZ-101 *in vivo* in extra-muscular tissues, including the central nervous system where *GYS1* is essential for glycogen production, is warranted. This is particularly important given that ERT does not cross the blood-brain barrier and that there is evidence of neurological involvement in Pompe disease (26-28). These considerations and cautionary approaches are needed not only for treating Pompe disease but also for individuals with other types of GSD.

In conclusion, targeting *GYS1* appears to be a promising approach to combat excessive muscle glycogen accumulation in Pompe disease. This small molecule approach combined with ERT may maximize the benefits of treatment and it may also reduce the dose and frequency of ERT. As far as we understand, MZ-101 does not cross the blood-brain barrier, and this remains a challenge for patients with Pompe disease. We remain cautiously optimistic about the potential use of *GYS1* reduction therapy in Pompe disease and other allied GSDs.

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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