Mannose-1-Phosphate Replacement Therapy: A Potential Treatment for PMM2-CDG

Abstract

Glycomine is developing GLM101, a mannose-1-phosphate (M1P) substrate replacement therapy, as a potential treatment for PMM2-CDG. Its development is supported by a clinical and preclinical dataset demonstrating:

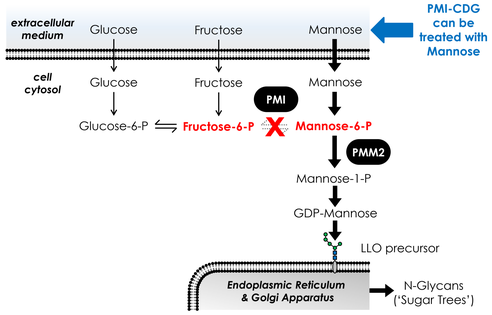
- ***Clinical proof-of-concept***—restoration of the same pathway with mannose is an effective therapy for PMI-CDG.
- ***Normalization of GDP-mannose***—GLM101 fully restores levels of GDP-mannose to normal in a dose-dependent manner.
- ***Efficacy across all genotypes***—GLM101 demonstrates robust efficacy in fibroblasts of all genotypes tested.
- ***Restoration of full-length glycoproteins***—GLM101 restores the glycoprotein ICAM-1 in a dose-dependent manner.
- ***Uptake of M1P in vivo***—GDP-mannose in normal (wildtype) mouse blood is 30-50% derived from GLM101 administered via IV injection, demonstrating uptake into the N-glycan pathway.

Taken together, the data indicates GLM101 has the potential to treat PMM2-CDG. Clinical testing in healthy volunteers is underway and patient trials are scheduled to begin in 2022.

Data & Results

Clinical Proof-of-Concept

PMI-CDG can be successfully treated[1],[2] by administering oral doses of mannose—which restores signaling in the same pathway that is restored by Glycomine's therapy.

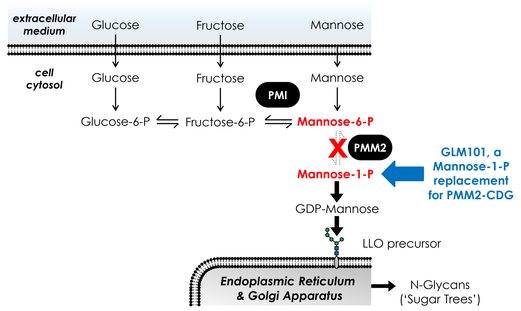


Following initiation of oral mannose therapy, PMI-CDG patients show improvements in biochemical markers and resolution of clinical symptoms:

- Within 1-3 months, biochemical markers are restored to normal levels; in particular, coagulation factors such as AT-III and Protein C, as well as other glycoproteins and albumin,
- Also within 1-3 months, clinical improvements are seen, such as a resolution of gastrointestinal symptoms and chronic diarrhea, as well as a return to normal glycemic control, and
- Over the longer term, patients return to normal feeding, weight gain and growth.

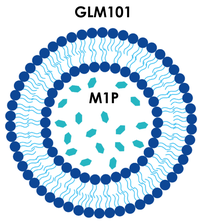
GLM101 bypasses the deficiency in the PMM2 enzyme and restores signaling in the same pathway where mannose is effective in the treatment of PMI-CDG.

For PMM2-CDG, signaling in the pathway needs to be restored downstream of PMM2 and M1P delivered to the cell cytosol.



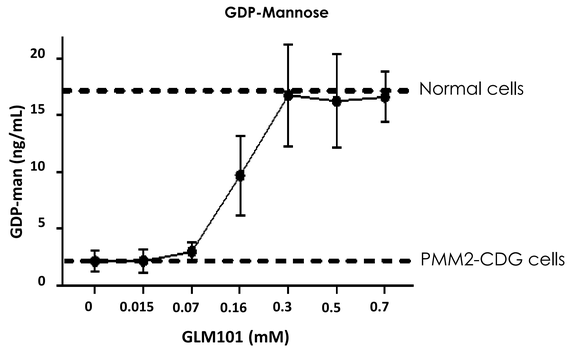
GLM101 consists of M1P encapsulated in a lipid nanoparticle (LNP), which protects the M1P from degradation in the systemic circulation and enables it to cross the cell membrane and access the cell cytosol—the exact location where it is required to replenish the deficiency in downstream substrates brought about by the reduced activity of the PMM2 enzyme.

- M1P resides within the LNP core, to protect it from degradation in the circulation.
- The LNP enables transport across a cell membrane and delivery to the cell cytosol.



Normalization of GDP-Mannose

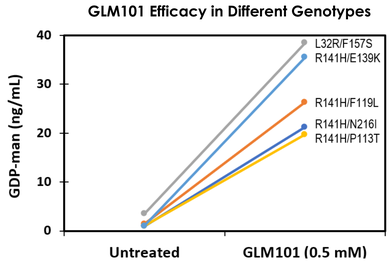
Reduced activity of PMM2 results in a deficiency of M1P and, as a consequence, the downstream substrate, GDP-mannose. Patient fibroblasts (R141H/F119L genotype) have 5-10% of normal GDP-mannose. Incubation with GLM101 restores GDP-mannose to normal levels in a dose-dependent manner.



Source: All patient fibroblast cells were obtained from the Corriell Institute.

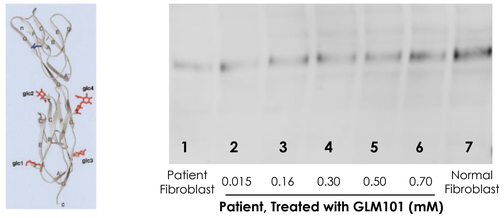
Efficacy Across All Genotypes

GLM101 bypasses the deficiency in the PMM2 enzyme and, as such, the approach is effective regardless of the genotype. We have seen robust efficacy across all patient genotypes tested—with an average increase in GDP-mannose of 20-fold (2,000%).



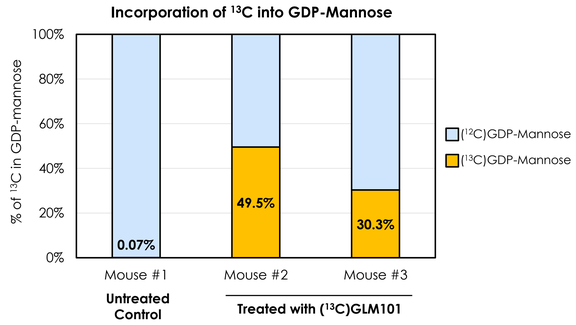
Restoration of Full-Length Glycoproteins

In addition to restoring GDP-mannose, GLM101 also restores full-length glycoproteins. ICAM-1 is a protein that regulates the immune system and is heavily glycosylated—with 4 glycans. It is deficient in PMM2-CDG patient fibroblasts (column #1, below) and is restored by GLM101 in a dose-dependent manner (columns #2 to #6) to approach normal levels (column #7).



Uptake of M1P In Vivo

GDP-mannose extracted from mouse whole blood after 3 weeks of dosing shows that the exogenously dosed (^{13}C-labelled) M1P entered the N-glycan biosynthetic pathway and can be utilized by the mice to synthesize the downstream substrate, such that 30-50% of the GDP-mannose is comprised of ^{13}C derived from GLM101 administered exogenously via IV injection.



Clinical Trials

Glycomine has an ongoing Natural History study in PMM2-CDG patients. A Phase 1 clinical study in healthy volunteers is also ongoing. Phase 2 studies in PMM2-CDG patients are planned to start in 2022.

Natural History Study (GLY-000)

Glycomine is sponsoring a Natural History study in 11 sites in the US and Europe (3 in the US, 8 in Europe) that has enrolled 139 PMM2-CDG patients. The goal is to provide information about the longitudinal course of the disease and help to select biomarkers and clinical endpoints for future investigational trials.

Additionally, this trial has improved the current standard-of-care in treating PMM2-CDG patients—having identified that a significant portion of patients are at risk of adrenal insufficiency, meaning they cannot efficiently produce cortisol in response to stress and, as a result, are at risk of sudden death in stressful situations. The findings were published in 2021[3].

Phase 1 Trial – Healthy Volunteers

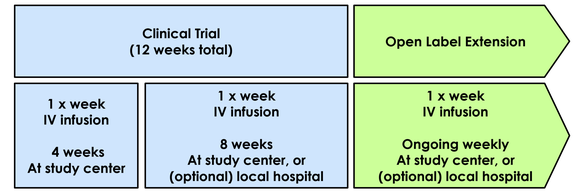
This trial began in December 2021 and is ongoing. There is both a single dose and multiple dose portion in this trial. The purpose is to explore the safety and tolerability of the therapy.

Phase 2 Trials – PMM2-CDG Patients

These are in planning and will enroll PMM2-CDG patients beginning in the second-half of 2022. The purpose is to explore the safety and tolerability of the therapy and, secondarily, explore the impact of GLM101 on multiple biomarkers of disease.

Adult patient trial – US & Europe (see below):

- Will enroll patients in the US and Europe to receive varying doses of GLM101 for up to 3 months, and
- All patients that are getting benefit from the therapy—at their choice—will be able to continue to receive drug as part of an open-label extension.



Pediatric patient trials are planned to begin in Europe in 2022, subject to ongoing European Medicines Authority (EMA) regulatory feedback, and in the US in 2023.

References

1. *R. Niehues, et al., J. Clin. Invest., Vol. 101, 7, 1414 (1998)*
2. *H.K. Harms, et al., Acta Paediatr, Vol. 91, 1065 (2002)*
3. *A. Cechova, et al., Mol. Gen. & Metab., Vol 133, 397 (2021)*