Glycomine's Natural History Study Informs Potentially Lifesaving Update to Standard of Care for PMM2-CDG Patients

- *International, multi-center study indicates that PMM2-CDG patients may be at risk for adrenal insufficiency, a previously unknown feature of PMM2-CDG*
- *Monitoring of morning cortisol and ACTH levels should be part of the standard of care in PMM2-CDG patients, and glucocorticoid replacement therapy may be critical during times of stress or illness*
- *Glycomine plans to initiate by the end of the year the first interventional clinical trial of GLM101, a mannose-1-phosphate replacement therapy designed to address the underlying deficiency in PMM2-CDG*

SAN CARLOS, Calif., June 29, 2021 – Glycomine, Inc., a biotechnology company focused on developing new therapies for orphan diseases, today announced the publication in Molecular Genetics and Metabolism of a key finding from a natural history study of phosphomannomutase 2-congenital disorder of glycosylation (PMM2-CDG), a rare pediatric orphan disease. In this study, the levels of morning cortisol and adrenocorticotropic hormone (ACTH) were measured in a cohort of patients and found to be significantly below normal, indicating PMM2-CDG patients are at risk for secondary adrenal insufficiency. These data provide key insights to improve standard of care, as early recognition of adrenal insufficiency and initiation of glucocorticoid replacement therapy and stress dosing could be lifesaving. The authors conclude that morning cortisol and ACTH levels should be evaluated at least annually for all patients with PMM2-CDG. If abnormal, a low dose ACTH stimulation test should follow to evaluate the hypothalamus, pituitary, adrenal (HPA) axis.

"Endocrinopathies in PMM2-CDG have not received the attention they deserve, especially considering that glycoproteins are involved in virtually every endocrine axis," said Kyriakie Sarafoglou, M.D., Associate Professor in the Department of Pediatrics at University of Minnesota and lead author of the paper. "Through an international collaboration, this study was the first to identify that patients with PMM2-CDG are at risk for secondary adrenal insufficiency and to suggest that morning cortisol and ACTH monitoring should become part of standard care in these patients."

The natural history study completed enrollment with 139 PMM2-CDG patients at 11 sites around the world (ClinicalTrials.gov Identifier: NCT03173300). Morning serum cortisol and ACTH levels were simultaneously measured in a cohort of 43 patients. In this cohort, 11 patients (25.6%) had cortisol below 5 µg/dl and low to normal ACTH levels, suggestive of secondary adrenal insufficiency. Secondary adrenal insufficiency has a prevalence of 1.5 to 2.8 in 10,000 (< 0.03%) in the general population. Since this finding, two of the 11 patients have been confirmed to have central adrenal insufficiency after low dose ACTH stimulation test results and are on hydrocortisone replacement and/or stress dosing during illness.

"We initiated this natural history study, which is the largest longitudinal study ever undertaken for this disease, to learn more about how PMM2-CDG affects patients and inform the design of our clinical trials for GLM101," said Horacio Plotkin, M.D., FAAP, Chief Medical Officer of Glycomine. "Through thoughtfully and scientifically studying the clinical presentation and biochemistry of PMM2-CDG, our investigators have uncovered a significant risk factor that is often masked by other co-morbidities of the disease. We thank the investigators and the patients and families who participated in this study for their time and support as we advance into clinical trials GLM101. Good things happen when patients and families, investigators, and companies work together."

"Even before we have started our first interventional clinical trial, we have uncovered a potential life-saving therapeutic intervention," said Peter McWilliams, Ph.D., CEO of Glycomine. "While cortisol/ACTH monitoring and glucocorticoid therapy have the potential to be lifesaving for PMM2-CDG patients during stress or illness,

they are still only addressing the symptoms of the disease. We look forward to initiating later this year our interventional clinical trials for GLM101 that has the potential to restore the deficiency in mannose-1-phosphate that causes PMM2-CDG."

The research entitled, "Should patients with Phosphomannomutase 2-CDG (PMM2-CDG) be screened for adrenal insufficiency?" is available at this link: https://doi.org/10.1016/j.ymgme.2021.06.003.

About PMM2-CDG (CDG-Ia)
PMM2-CDG (phosphomannomutase 2-congenital disorder of glycosylation), previously known as CDG Type Ia, is the most prevalent of the more than 100 different congenital disorders of glycosylation (CDG). CDGs result in defective formation of the glycan chains essential for the structure and function of glycosylated proteins that represent as many as 50% of all proteins in the body. PMM2-CDG is caused by a deficiency of the enzyme phosphomannomutase 2 (encoded by the *PMM2* gene). The disease is a severe multisystem disorder with symptoms such as coagulopathies, endocrinopathies, hypotonia, stroke-like episodes, as well as immune and nervous system disfunctions, and resulting mortality of 20% in the early years of life.

About GLM101, a Potential Treatment for PMM2-CDG
Glycomine's GLM101 is a mannose-1-phosphate replacement therapy in development to treat PMM2-CDG, a disease caused by a deficiency of the enzyme phosphomannomutase 2 (PMM2). PMM2 converts mannose-6-phosphate to mannose-1-phosphate, which is an essential sugar molecule in the N-glycosylation pathway and is crucially important for proper glycoprotein structure and function. GLM101 is designed to deliver mannose-1-phosphate directly into cells and thereby bypass the PMM2 enzyme deficiency and address all disease-causing PMM2 mutations to restore pathway function. GLM101 has received Orphan Drug Designation in the U.S. and Europe and Rare Pediatric Disease Designation in the U.S.

About Glycomine, Inc.
Glycomine is developing orphan drugs for serious rare disorders of metabolism and protein misfolding for which no other therapeutic options exist. The company's approach is to use replacement therapies – substrates, enzymes, or proteins – and to target those molecules to clinically relevant cellular compartments. The company is based in San Carlos, California and supported by leading international life sciences investors. For more info, visit www.glycomine.com.

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