# Glycogen storage disease type 1a (GSD1a) (mRNA-3745)

**Last program update: October 29, 2020**

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mRNA-3745 nominated as fourth systemic intracellular therapeutics DC
Glycogen storage disease type 1a (GSD1a) overview

**New intracellular therapeutics DC – mRNA-3745**

- **GSD1a** is a rare inherited metabolic disease resulting from a deficiency in the metabolism of glucose, due to mutations within the enzyme glucose 6-phosphatase, G6Pase

- **Disease burden:** Life-threatening hypoglycemia, long-term liver & kidney damage

- **Target population:** Incidence of ~1:100k live births
  - 2,500 patients in US¹, and >4,000 patients in the EU¹

- **Standard of care:**
  - Strict diet control
  - Frequent consumption of uncooked cornstarch to improve hypoglycemia

**Moderna concept:** IV-administered mRNA encoding G6Pase enzyme to restore deficient or defective intracellular enzyme activity

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¹ Based on estimated incidence of 1:100,000
Glycogen storage disease type 1a (GSD1a) overview

Defect in G6PC gene disrupts glucose metabolism pathways

- Missing or defective G6Pase leads to:
  - Hypoglycemia
  - Lactic acidemia
  - Hyperlipidemia

- Metabolite buildup associated with hepatomegaly, hepatocellular adenomas, and higher risk of liver cancer

- Restoring G6Pase activity should increase blood glucose levels, decrease uric acid, lactic acid, triglyceride levels
Glycogen storage disease type 1a (GSD1a) (mRNA-3745)
mRNA-encoded enzyme localized to endoplasmic reticulum
Glycogen storage disease type 1a (GSD1a) (mRNA-3745)

Preclinical data – restoration of enzymatic activity

**Study Design**

**Species:** Mouse

- Animals: Liver-Specific G6PC Knockout (L.G6PC -/-)
- Dose: 0.2, 0.5, 1.0 mpk
- Dosing Schedule: single dose
- Injection Route: IV
- Sample Size: 5-8

**Serum biomarkers after single dose of G6Pase mRNA**

- WT vs. L.G6PC -/-(mRNA (mpk)

**Reduction in liver weight 24 hours after IV administration of G6Pase mRNA**

- WT vs. L.G6PC -/-(%) of body weight

**Restoration of blood glucose above therapeutic threshold with repeat dosing of G6Pase mRNA**

- 1st Dose vs. 2nd Dose vs. 3rd Dose vs. 4th Dose vs. 5th Dose

**We have demonstrated preclinical proof-of-concept for G6Pase mRNA therapy in in vivo studies**

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*Not as: eGFP is a negative control. Asterisks based on one-way ANOVA and post-treatment vs. eGFP levels:
  *p<0.05
  **p<0.001
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