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Rare disease therapeutics

Program Pack

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

Glycogen storage disease type 1a (GSD1a) overview

GSD1a refers to a rare inherited metabolic disease resulting from a deficiency in the metabolism of glucose

GSD1a biology

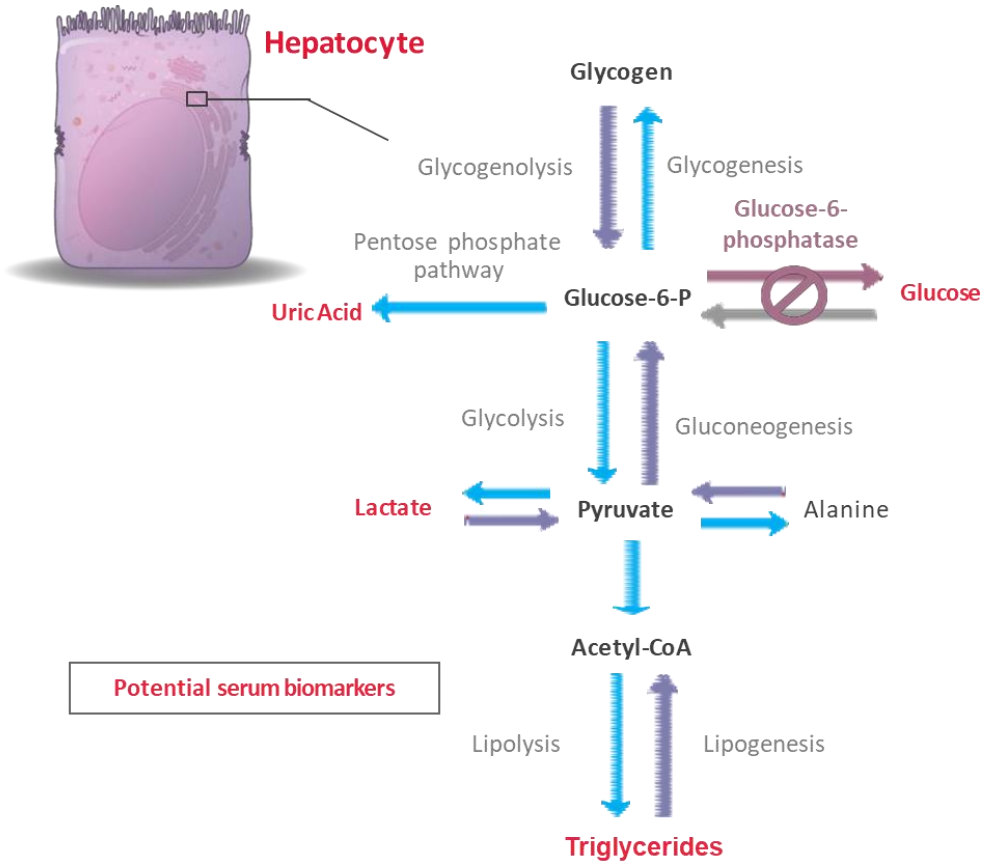
GSD1a is caused by mutations within the enzyme glucose 6-phosphatase, G6Pase

Clinical manifestations

- **Life-threatening** hypoglycemia, long-term liver & kidney damage
- **Long-term hepatic complications are observed in 75% of adult patients** of which 10% are at risk of malignant transformation into hepatocellular carcinomas (HCC)

Glycogen storage disease type 1a (GSD1a) overview

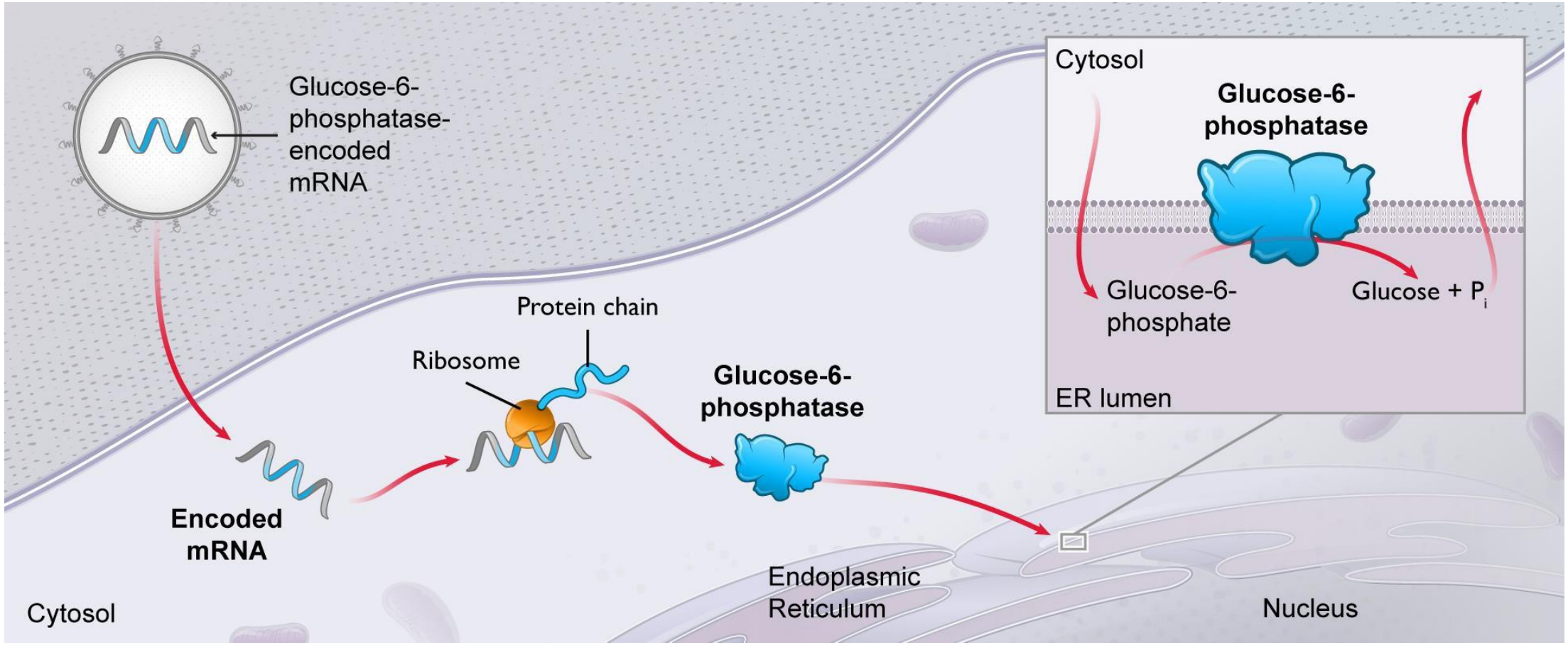
Significant unmet medical need



Standard of care

- **No approved therapy** for GSD1a
- Current interventions include:
  - **Strict diet control;** frequent consumption of uncooked cornstarch to improve hypoglycemia
  - Feedings by **gastric tube**
  - **Glycosade®** (cornstarch for dietary management)
  - **Liver/kidney transplantation**

GSD1a therapy (mRNA-3745) encodes for the G6Pase enzyme



Ongoing Phase 1/2 study of mRNA-3745 in GSD1a

Orphan Drug Designation granted by U.S. FDA

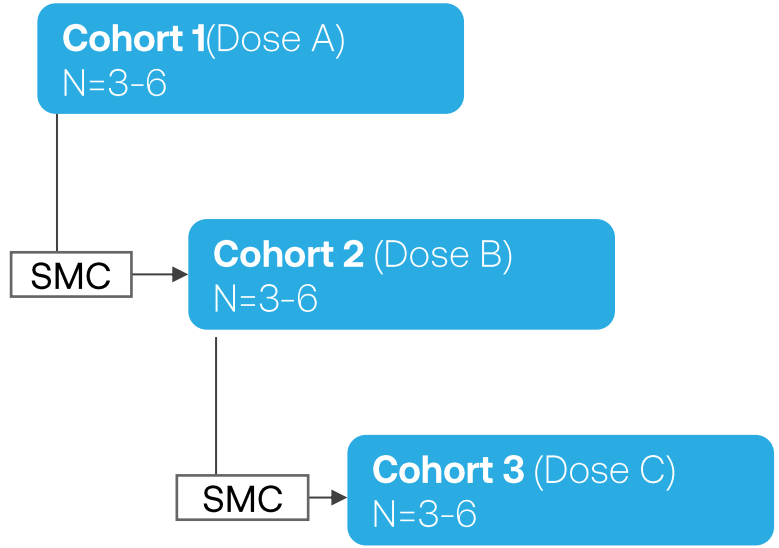
Evaluate the **safety and pharmacology** of mRNA-3745 in patients 18 years of age and older with GSD1a

Single ascending dose study: Challenging patients twice, on day 3 and day 8

- **Biomarkers:** blood sugar and lactate
- **Clinical:** improvement in fasting tolerance 3 days and 8 days after a single dose of mRNA-3745

Trial progress: Enrollment ongoing (first participant dosed in June ’22)

Phase 1/2 Trial Design



SMC: Safety monitoring committee

Safe first-in-human administration of mRNA-3745

Intravenous infusion of mRNA-3745 with LNP2 without pre-medication was very well tolerated with only mild AEs

Patient 1

- Female, 21 years old
- GSD1a diagnosed at 6 months of age, managed with cornstarch
- Genotype: c.379_380dup (homo)

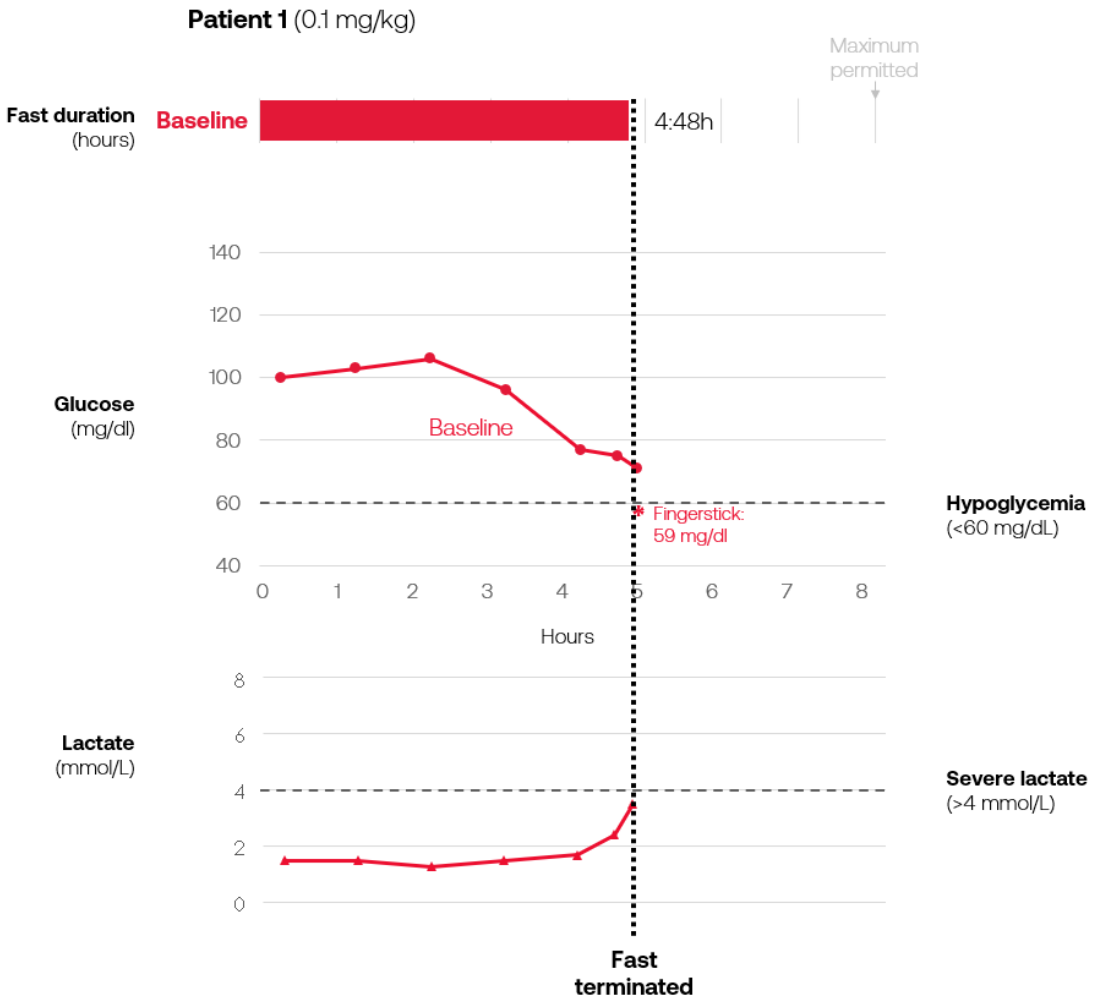
Patient 2

- Female, 18 years old
- GSD1a diagnosed at 2 years of age, managed with cornstarch
- Genotype: c.562G>C c.883C>T (compound het)

Safety

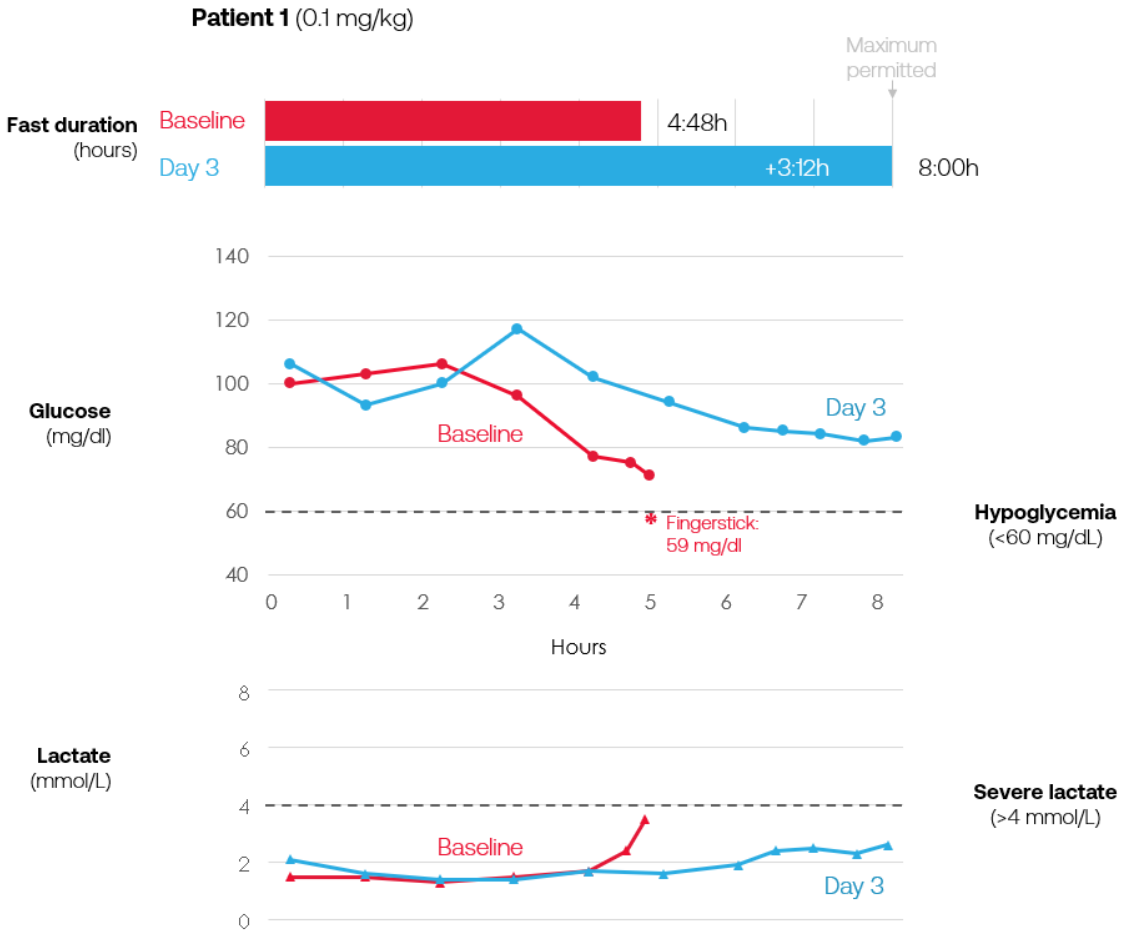
- No vital signs changes up to 12 hours post-infusion
- No serious adverse events
- No meaningful changes in safety labs, including hematology and liver function
- Follow up ongoing

Emerging efficacy data in GSD1a



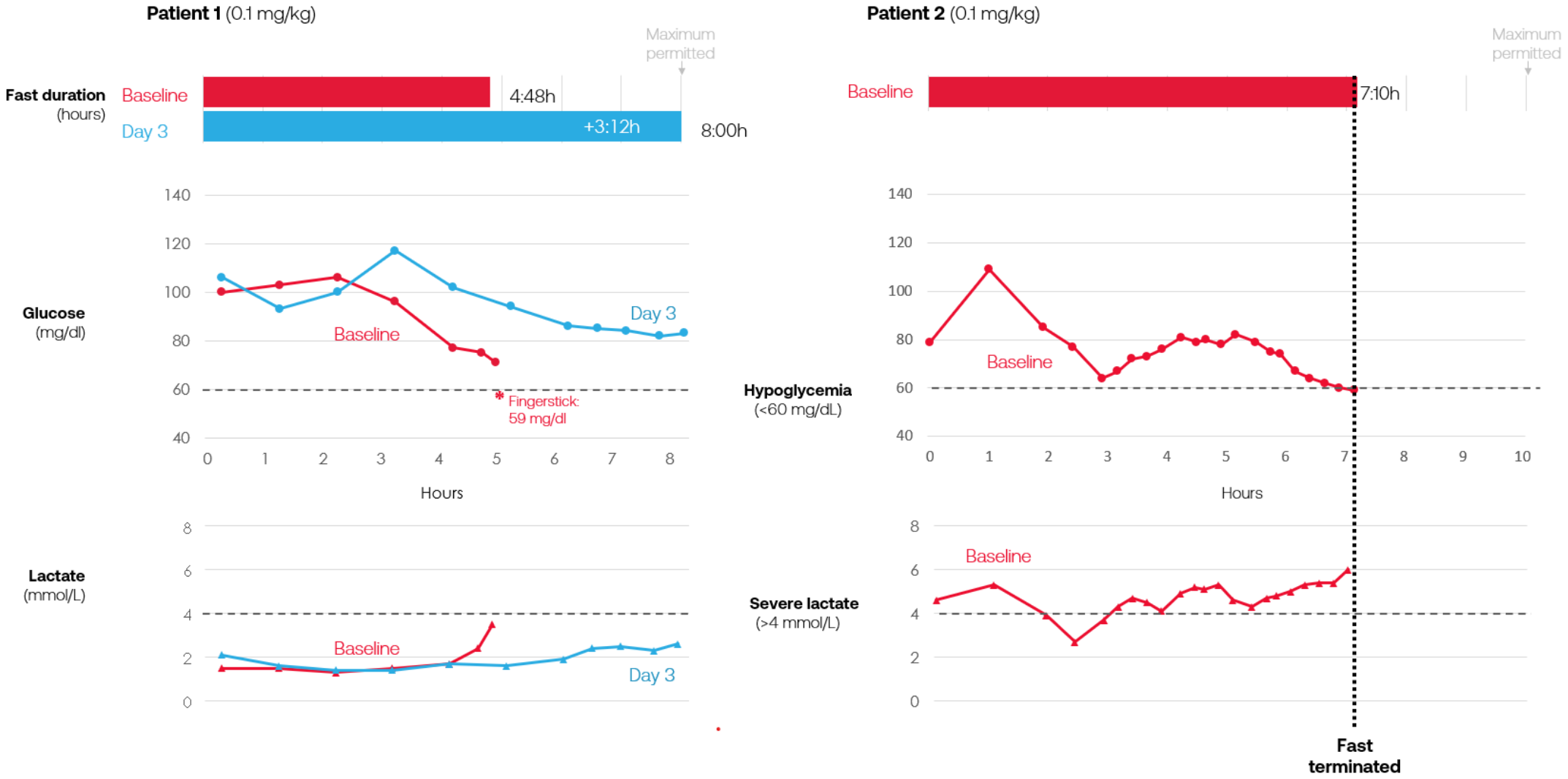
- Fast terminated due to confirmed hypoglycemia after clinical symptoms
- Evidence of severe metabolic strain with lactate approaching 4 mmol/L

Emerging efficacy data in GSD1a

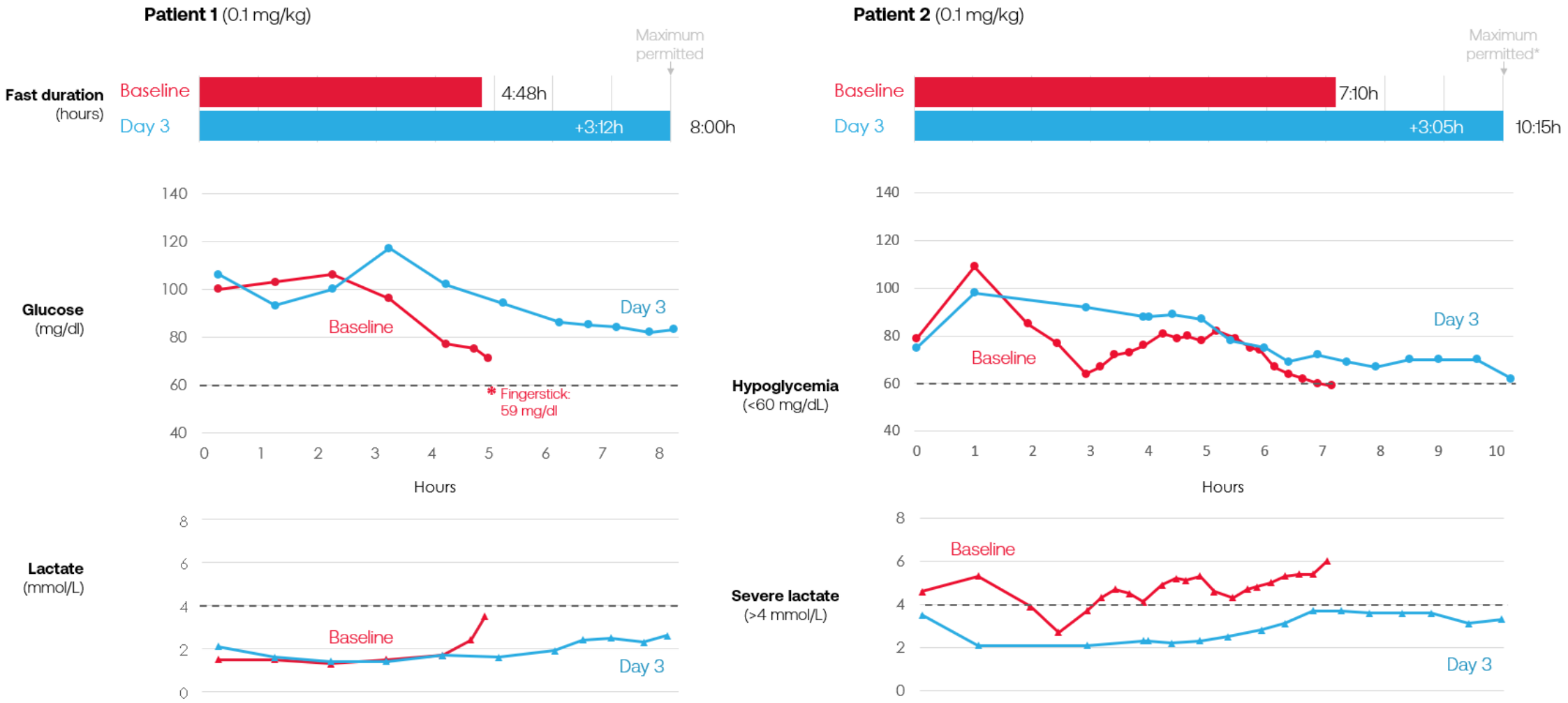


- Patient able to complete full fast (limited to 8 hours)
- Glucose and lactate maintained throughout the fast

Emerging efficacy data in GSD1a

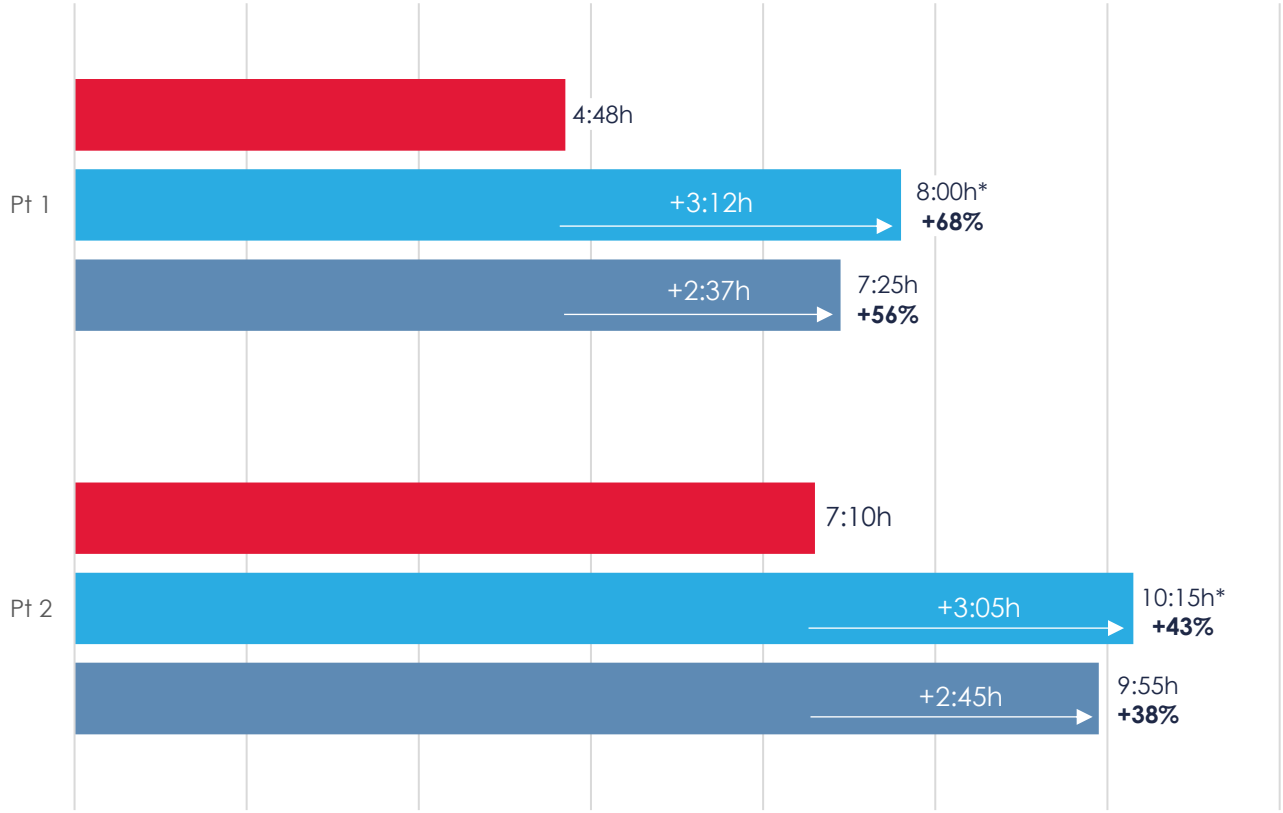


Emerging efficacy data in GSD1a



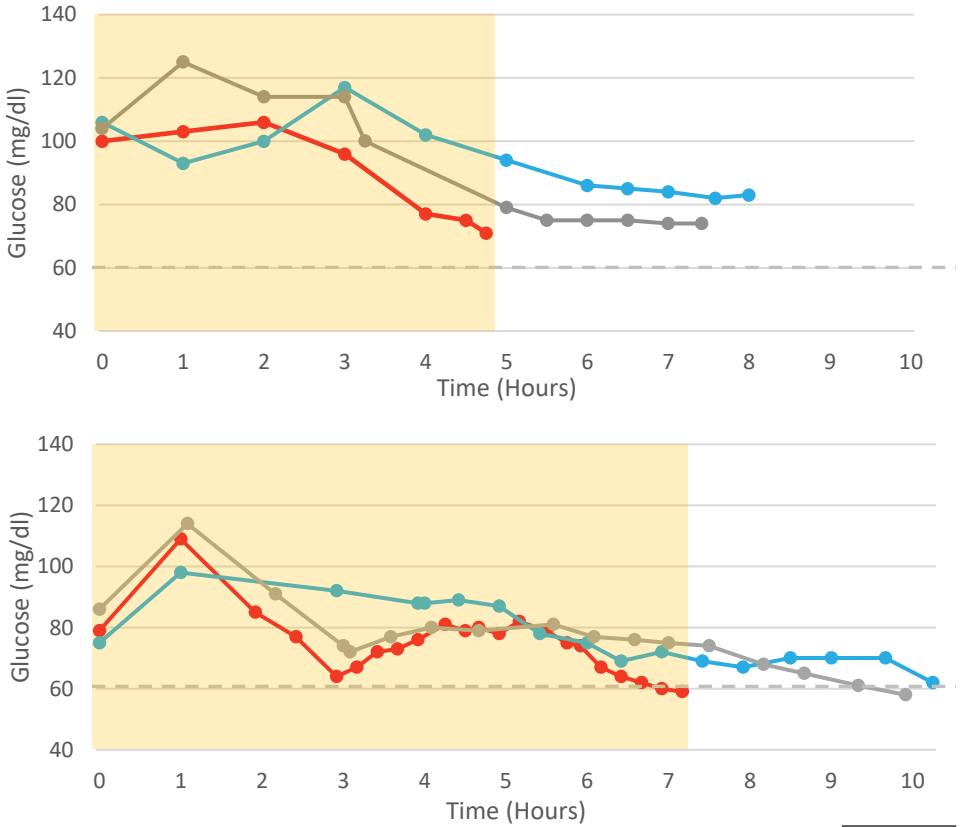
Improved fasting tolerance maintained through Day 8

Slight decrease vs. day 3, consistent with G6Pase enzyme half-life



Day -1
Day 3
Day 8

* Maximum Permitted



Day -1
Day 3
Day 8

mRNA-3745 for GSD1a – next steps

Continue to evaluate safety of mRNA-3745 and LNP2

Assess fast tolerance beyond day 8

Exploring higher doses to extend potential repeat dose interval

Identify a dose to move to repeat dose study

Forward-looking statement

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