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

Last updated: November 2nd, 2023

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines & therapeutics	Individualized neoantigen therapy (INT)	mRNA-4157						50-50 global profit sharing with **Merck**
	KRAS vaccine	mRNA-5671						Worldwide
	Checkpoint vaccine	mRNA-4359						Worldwide
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
Rare disease intracellular therapeutics	Propionic acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic acidemia (MMA)	mRNA-3705						Worldwide
	Glycogen storage disease type 1a (GSD1a)	mRNA-3745						Worldwide
	Ornithine transcarbamylase deficiency (OTC)	mRNA-3139						Worldwide
	Phenylketonuria (PKU)	mRNA-3210						Worldwide
	Crigler-Najjar syndrome type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge
Inhaled pulmonary therapeutics	Cystic fibrosis (CF)	VX-522						**Vertex** to pay milestones and royalties

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

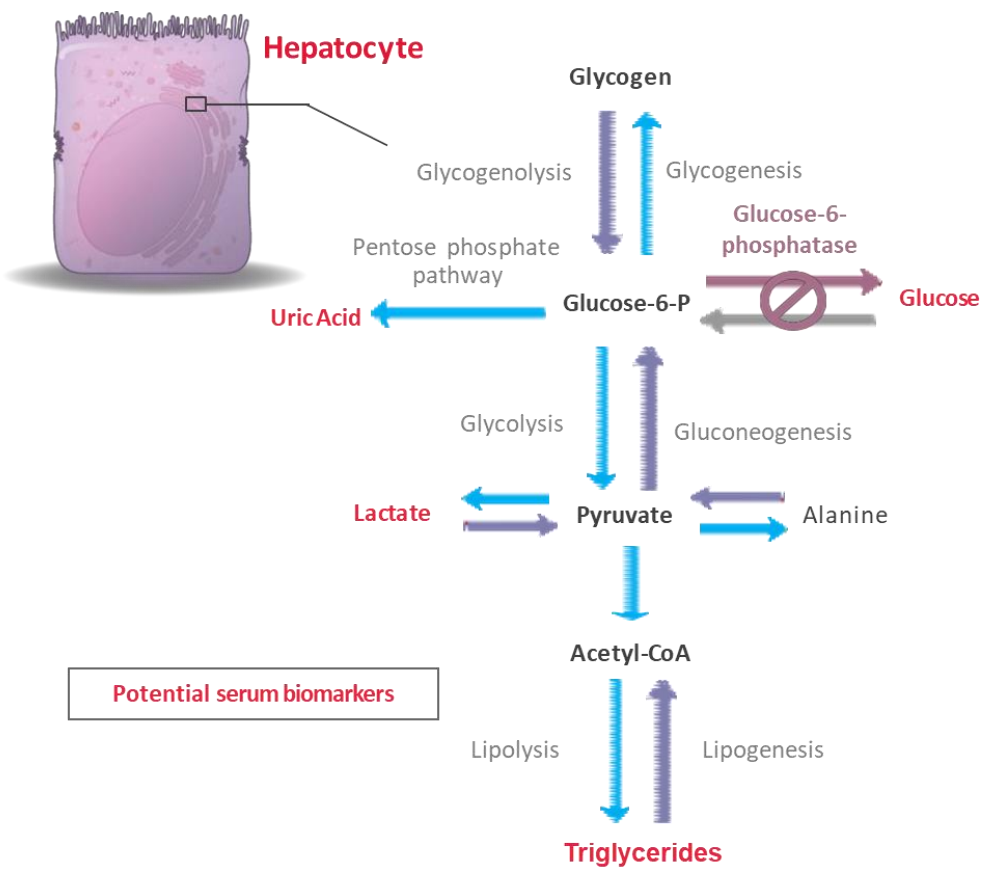
- GSD1a is caused by mutations within the enzyme glucose 6-phosphatase, G6Pase

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

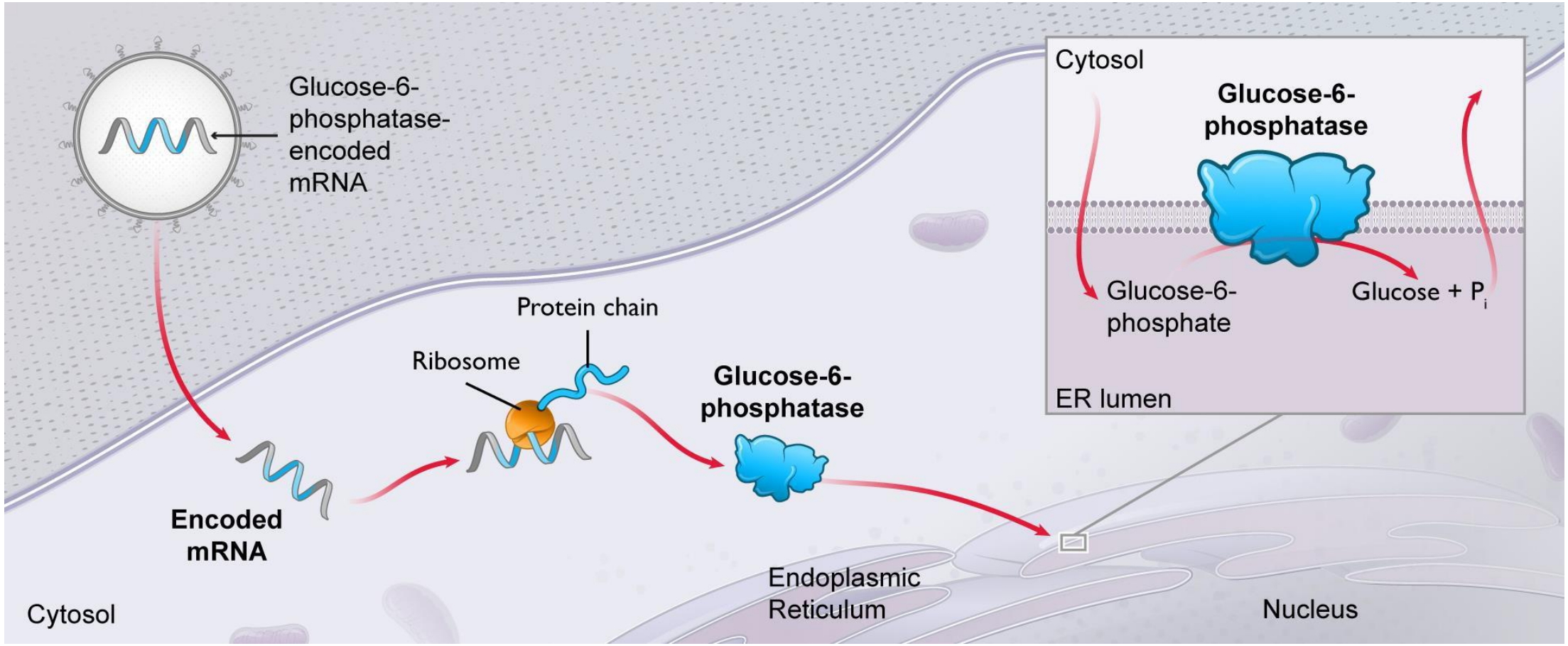
Significant unmet medical need



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

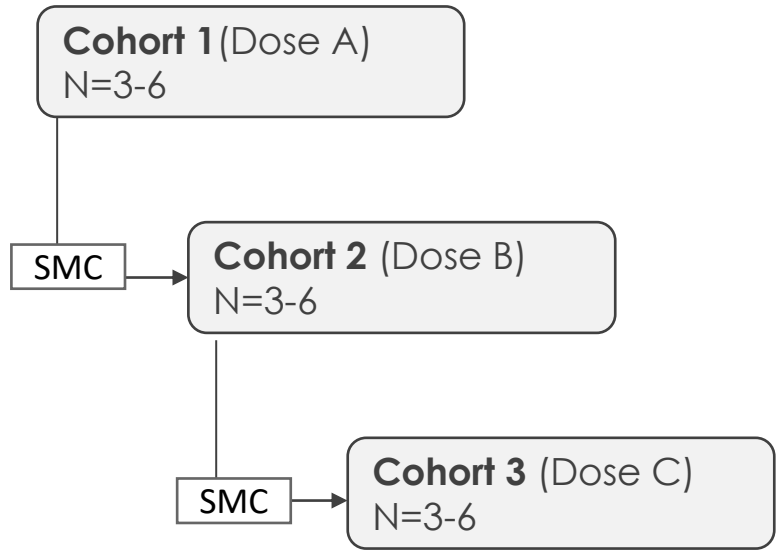
balance TRIAL

- 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

moderna

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)

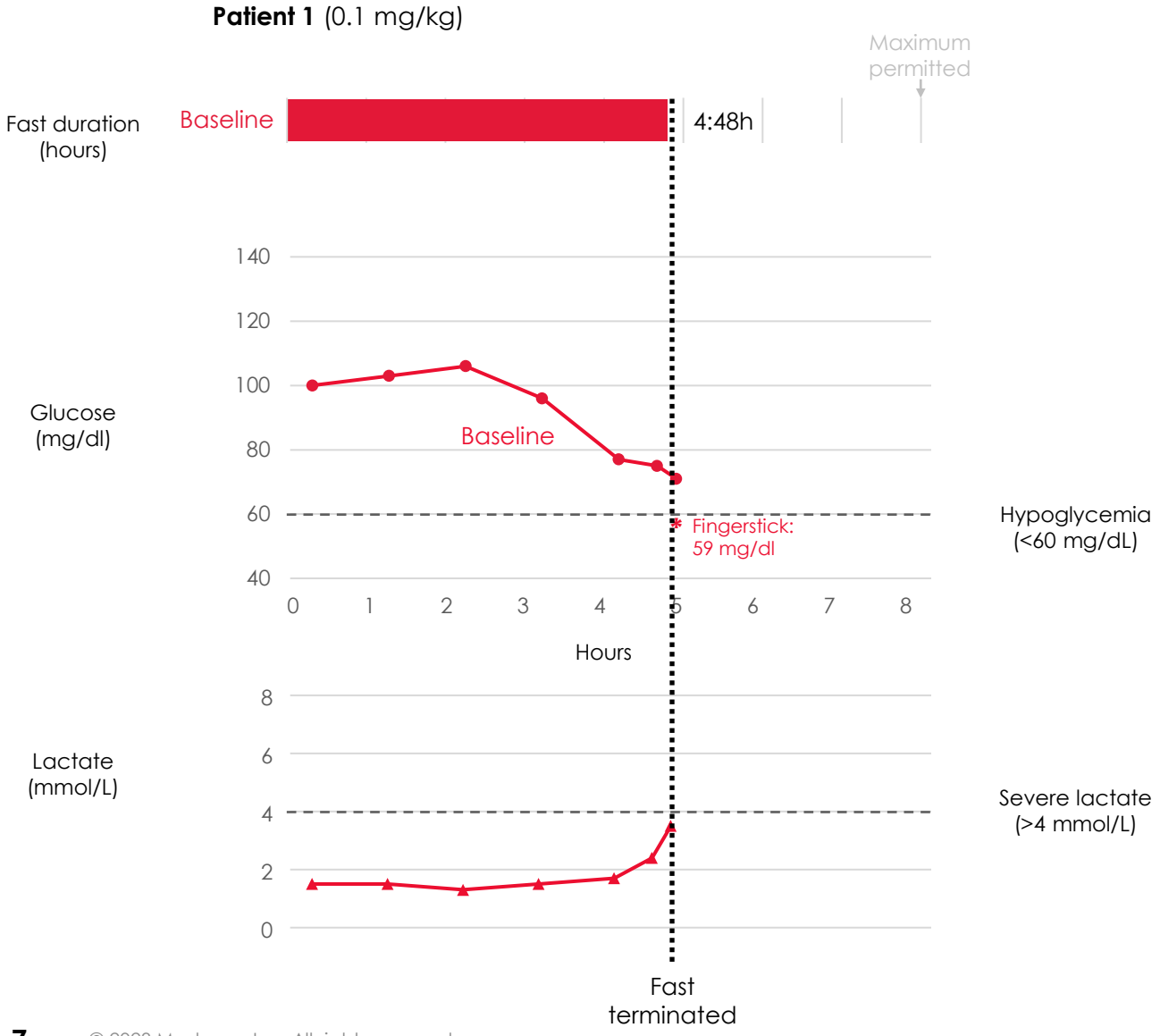
Patient 2

- 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

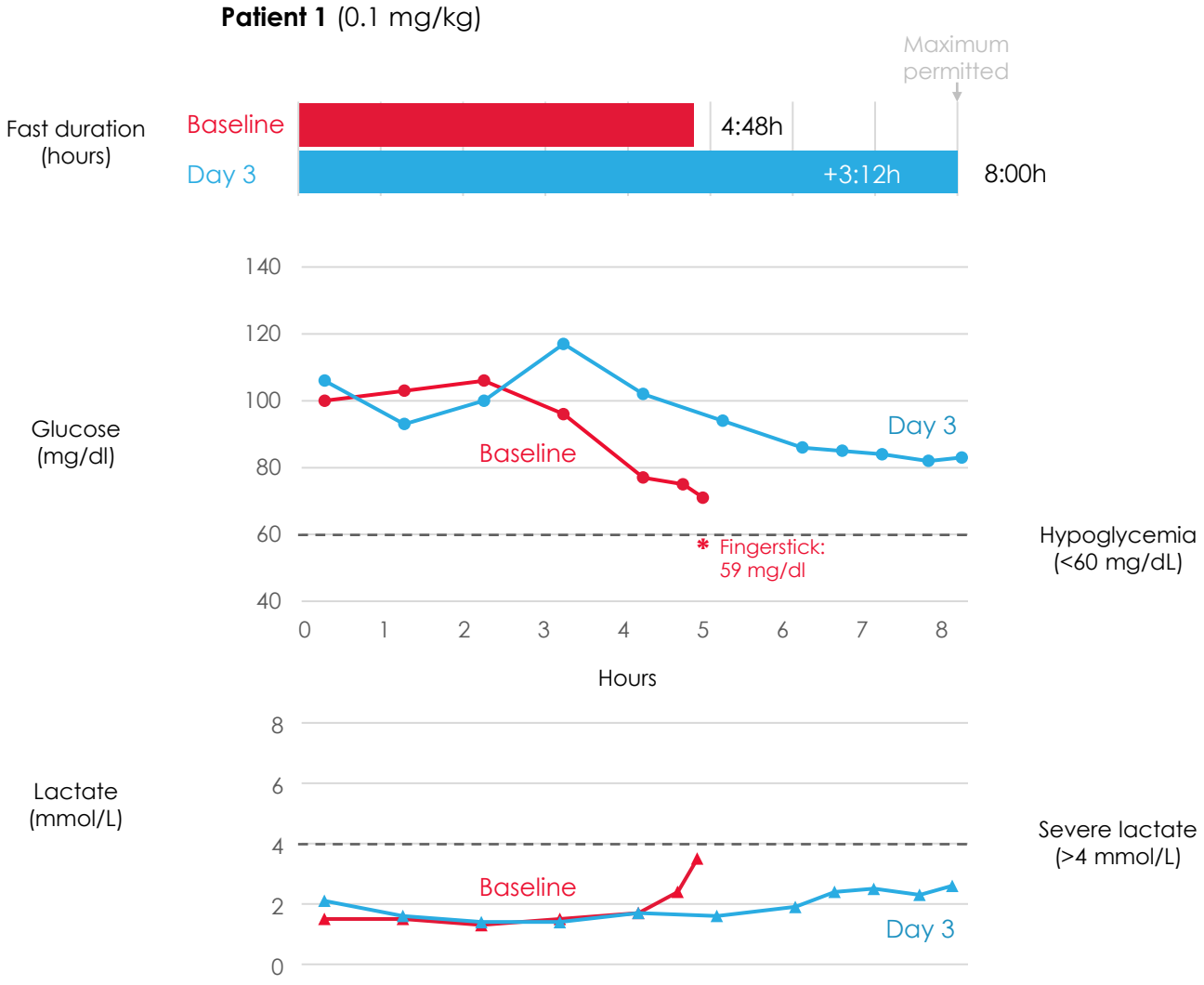
Emerging efficacy data in GSD1a



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



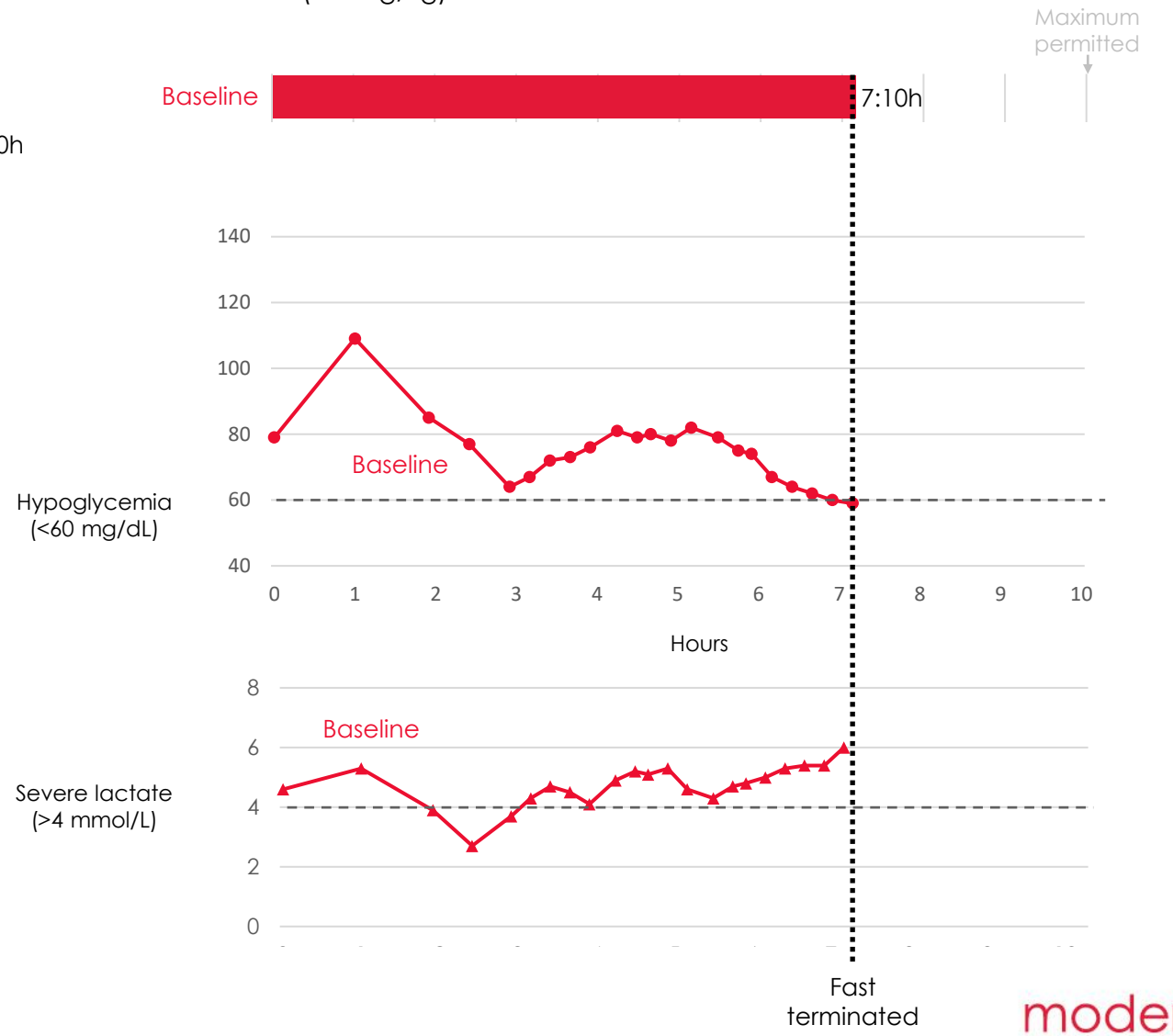
Patient able to complete full fast (limited to 8 hours)

Glucose and lactate maintained throughout the fast

Emerging efficacy data in GSD1a

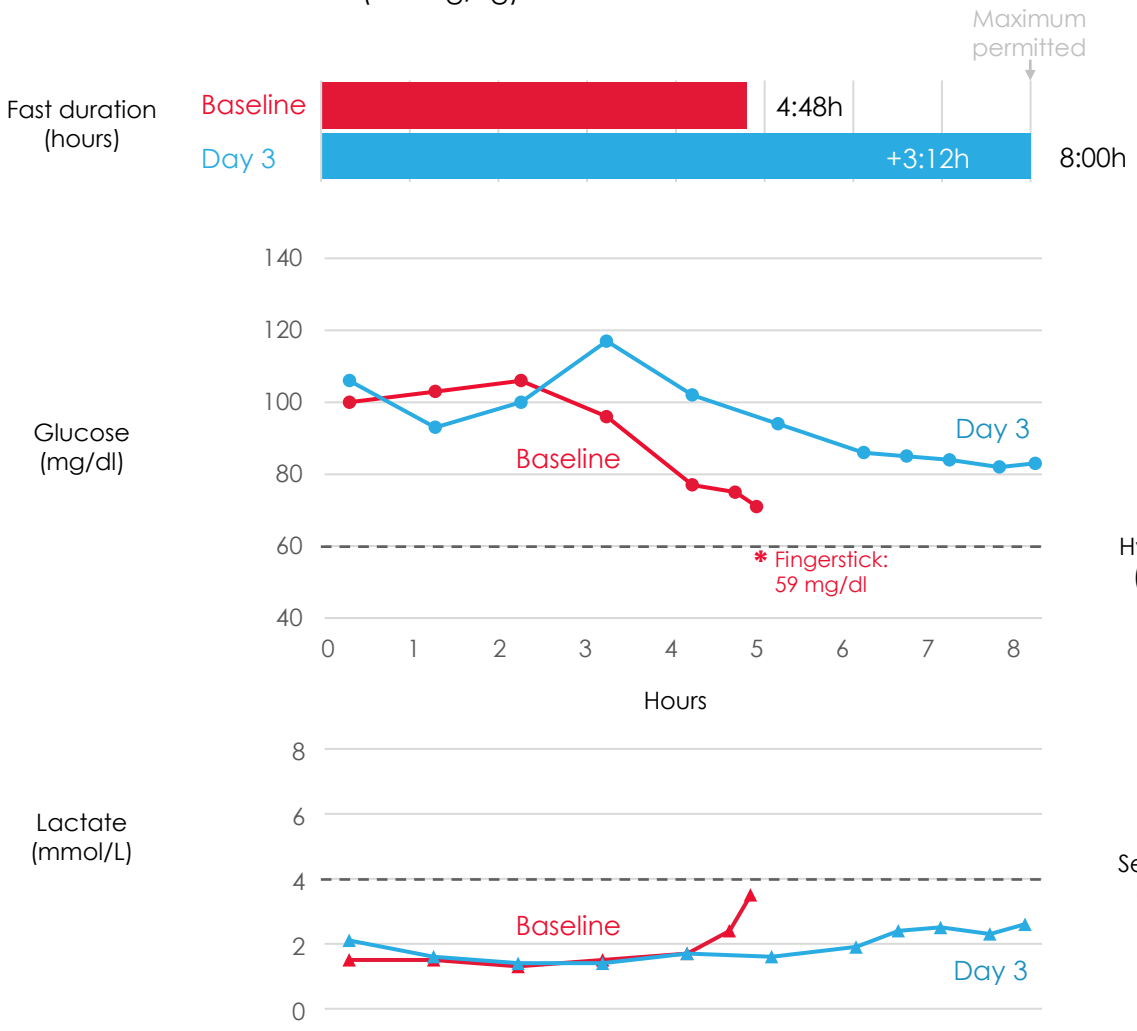
Patient 1 (0.1 mg/kg)

Patient 2 (0.1 mg/kg)

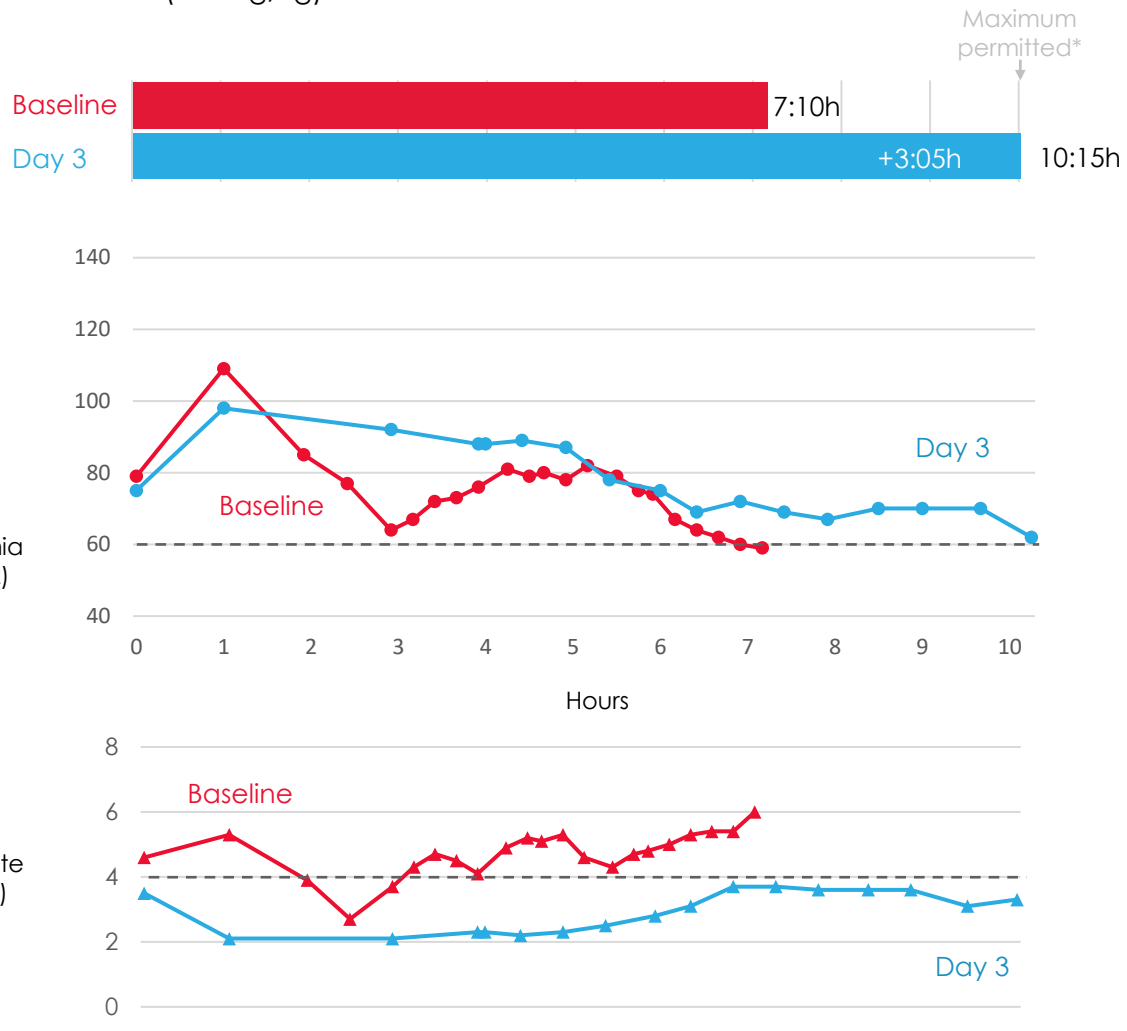


Emerging efficacy data in GSD1a

Patient 1 (0.1 mg/kg)

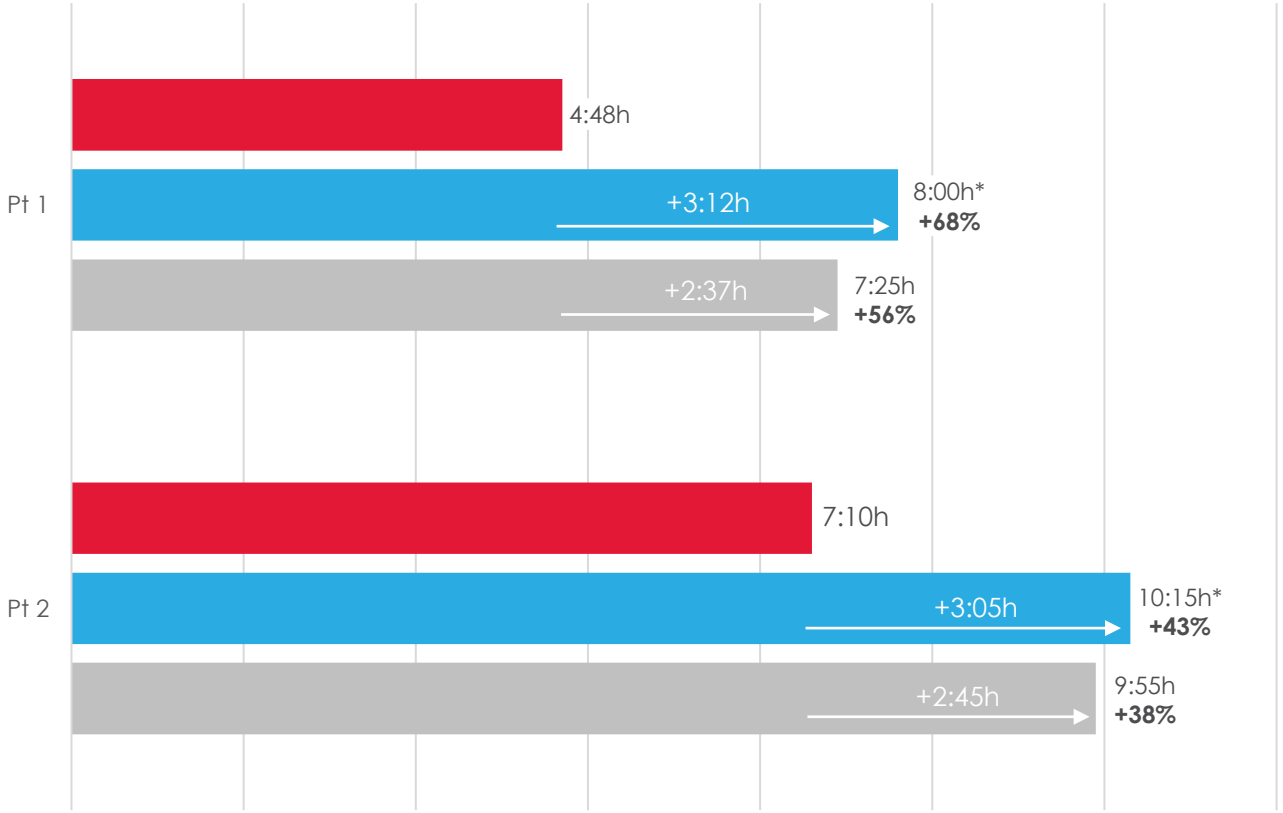


Patient 2 (0.1 mg/kg)



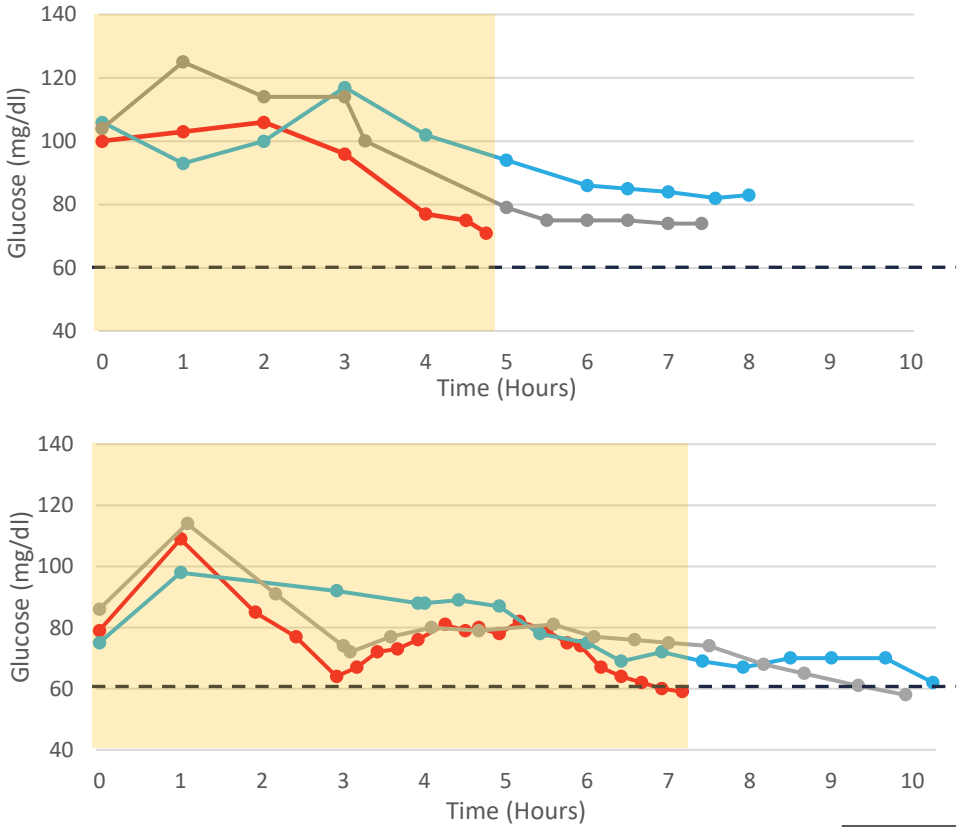
Improved fasting tolerance maintained through Day 8

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

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