moderna

Rare disease therapeutics

Program Pack

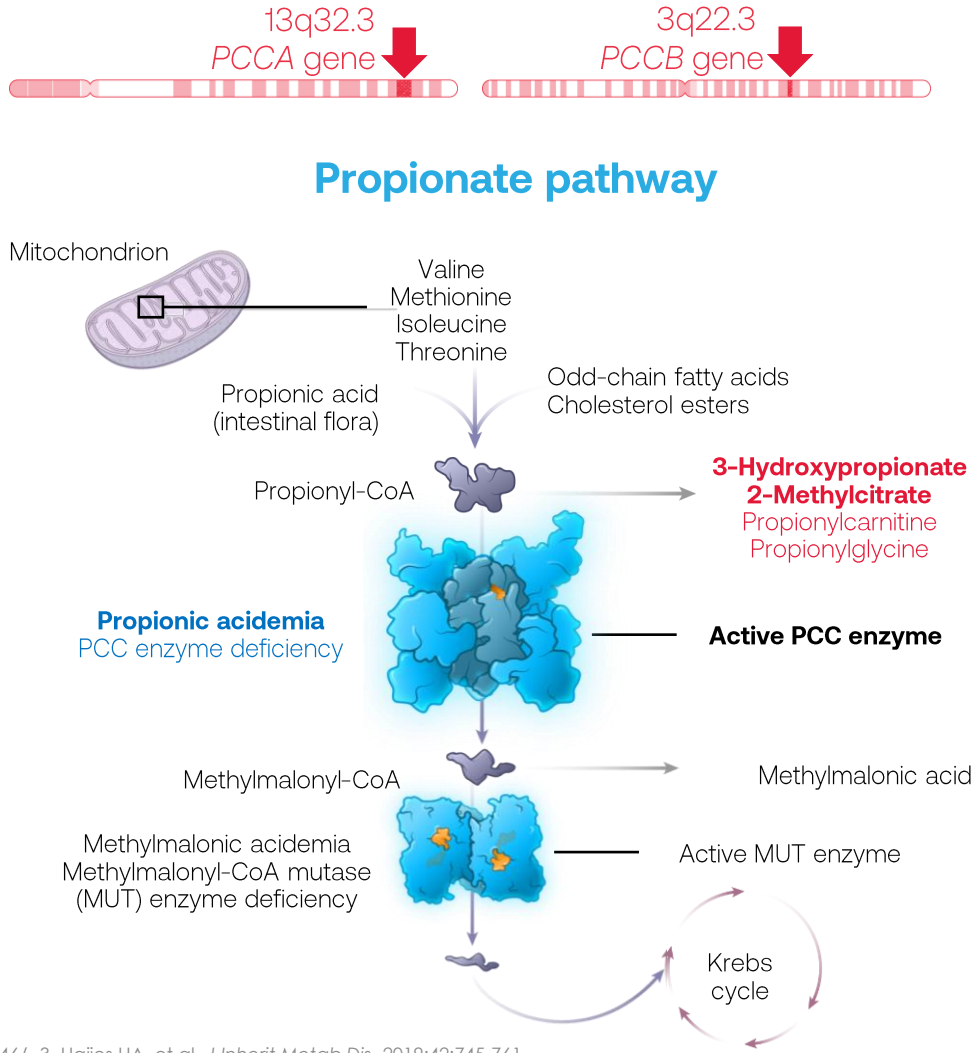
Propionic acidemia (PA) (mRNA-3927)

Propionic Acidemia (PA) Is a Rare Inherited Metabolic Disorder

Rare "intoxication-type" organic acidemia
Global birth prevalence estimates:
0.29–4.24 per 100,000 newborns[1]

Caused by pathogenic variants in *PCCA* or *PCCB* genes:
Deficiency of the mitochondrial enzyme propionyl-CoA carboxylase (PCC), an heterododecamer made up of alpha (PCCA) and beta (PCCB) subunits[2,3]

Accumulation of toxic metabolites,
including 2-methylcitrate (2-MC), and 3-hydroxypropionate (3-HP)[3]



1. Almasi T, et al. *Orphanet J Rare Dis.* 2019;14:40. 2. Shchelochkov OA, et al. In: GeneReviews®. https://www.ncbi.nlm.nih.gov/books/NBK92946/. 3. Haijes HA, et al. *J Inherit Metab Dis.* 2019;42:745-761.

Clinical Characteristics and Management of PA

Primarily a **pediatric disease**, with **onset typically in neonates** resulting in **significant morbidity and mortality**[1,2]

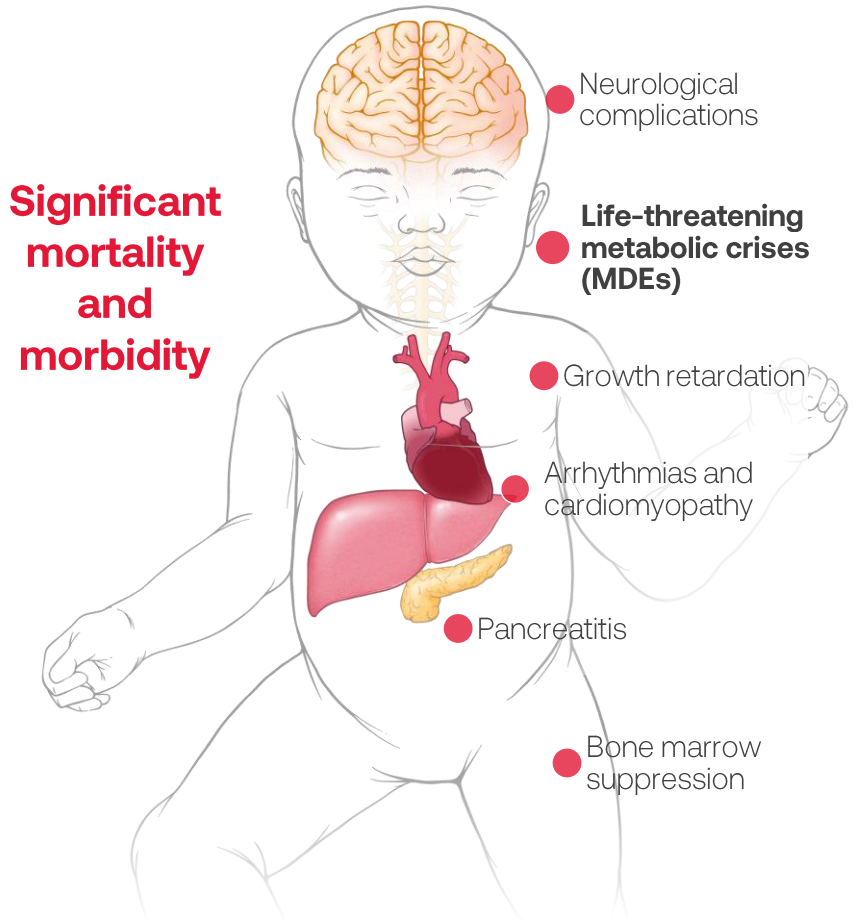
Characterized by recurrent, life-threatening metabolic decompensation events[1-3]

- Long-term cognitive outcome is negatively correlated to the number of metabolic decompensation events[4]

Multisystemic complications include neurological manifestations, cardiomyopathy, arrythmias, growth retardation, recurrent pancreatitis, bone marrow suppression, and predisposition to infection[1,2,5]

No approved therapies address the underlying defect in PA

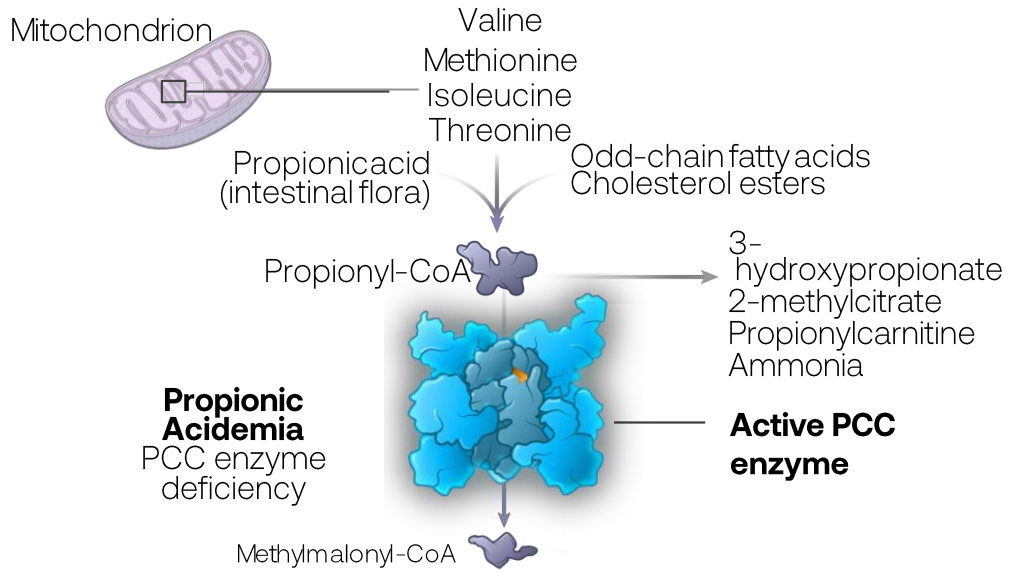
- Current management includes dietary protein restriction to reduce propiogenic precursors[3]
- Liver transplant improves biochemical and clinical outcomes; transplant is not curative



1. Shchelochkov OA, et al. In: GeneReviews®. https://www.ncbi.nlm.nih.gov/books/NBK92946/. 2. Fraser JL, et al. Curr Opin Pediatr. 2016;28:682-693. 3. Jurecki E, et al. Mol Genet Metab. 2019;126:341-354. 4. Grunert SC, et al. J Inherit Metab Dis. 2012;35:41-49. 5. Haijes HA, et al. J Inherit Metab Dis. 2019; 42:730-744.

PA therapy (mRNA-3927) encodes for an intracellular enzyme

Moderna's mRNA therapy for PA (mRNA-3927) encodes for two proteins that form the deficient enzyme



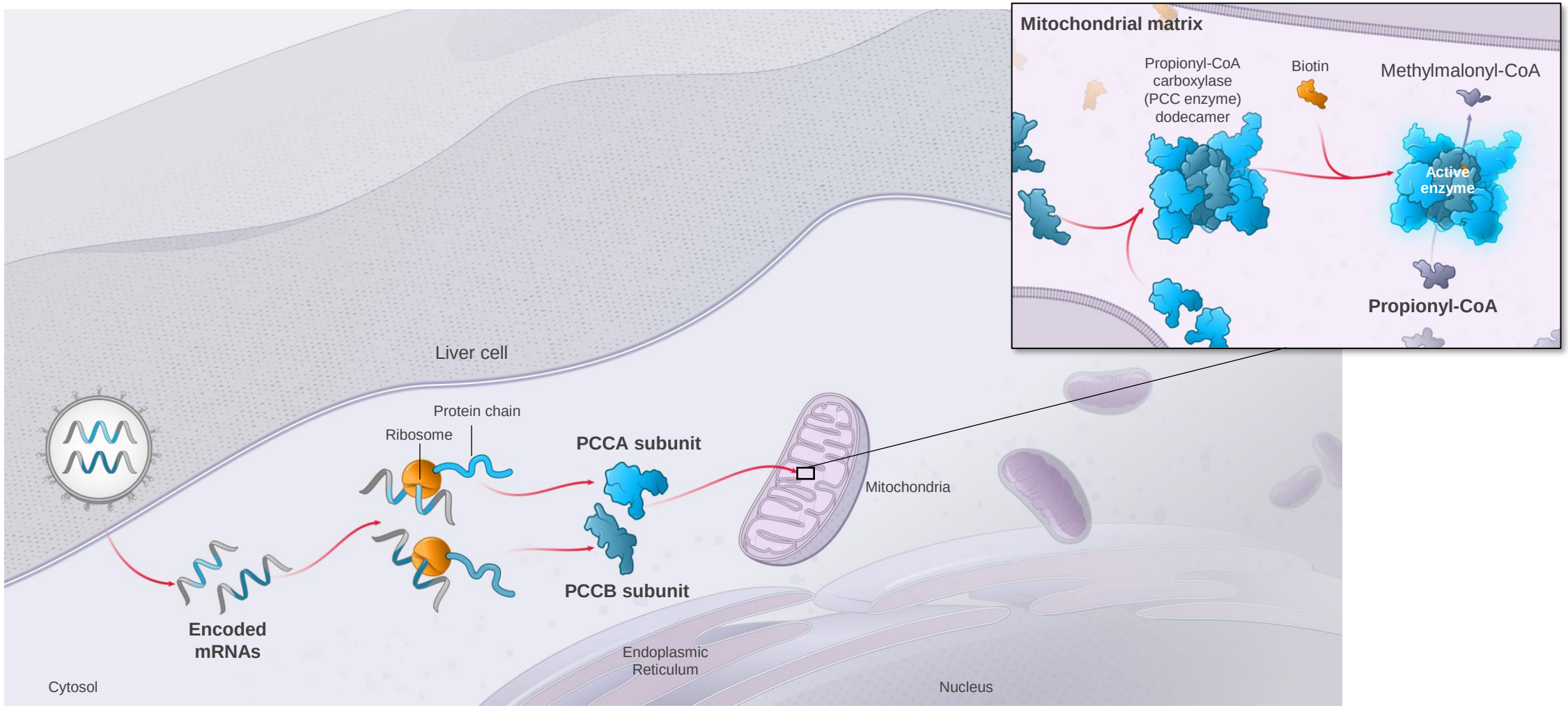
PA biology

Changes in the *PCCA* and *PCCB* genes cause propionic acidemia

- These genes provide instructions for making two parts (subunits) of the propionyl-CoA carboxylase enzyme
- Change in the *PCCA* or *PCCB* genes affect the normal function of the PCC enzyme and prevent the normal breakdown of propionyl-CoA

As a result, propionyl-CoA and other **harmful compounds** accumulate causing acute **metabolic decompensation** events and **damage to the brain** and other organs, causing the serious health problems associated with propionic acidemia

mRNA-3927 encodes for PCCA and PCCB subunit proteins to form an active PCC enzyme



R&D Day 2024 update

Ongoing Phase 1/2 study designed to evaluate safety and pharmacology of mRNA-3927 in participants with PA

Arm 1 enabled dose selection, enrollment is ongoing in Arm 2 dose expansion, and Arm 3 infant cohort

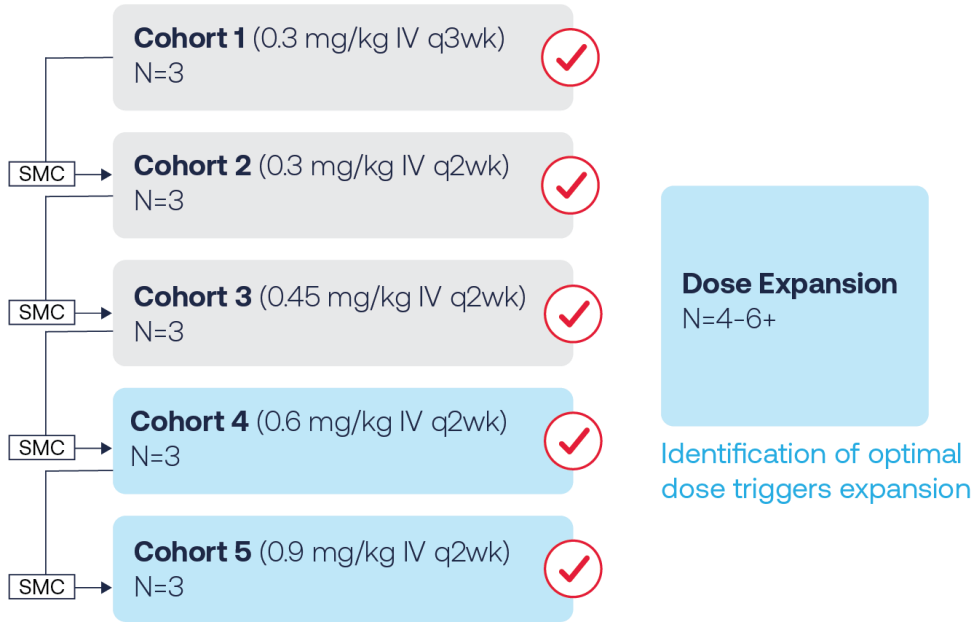
Primary endpoints: Safety and PK/PD

Secondary endpoints: Incidence and severity of adverse events and change in plasma biomarkers (Hydroxypropionic acid (3-HP) and methylcitric acid (2-MC))

Exploratory clinical endpoints: Metabolic decompensations events (MDE), cardiac function, quality of life

Current demographics: Participants aged 1-26 have been enrolled; 13 participants have completed the study

Phase 1/2 Trial Design (3 + 3 design)



PA: mRNA-3927-P101 Study Design

PART 1: Dose Optimization

Patients enrolled to better understand the dose

Participants ≥ 1 Year of Age
N=22

PART 2: Dose Expansion

Patients enrolled to better understand efficacy

Participants ≥ 1 Year of Age
N=15

PART 3: Infants

Patients enrolled to expand age cohort to include infants

Participants <1 Year of Age
N=10

PA: Overall Phase 1/ 2 clinical experience

As of August 22, 2024, 22 participants have been dosed

Thirteen participants have >1 year of dosing

31.3 cumulative patient-years of experience on study drug

Longest duration of treatment is 3.1 years and median duration 1.45 years

Over 722 intravenous doses administered

Study is ongoing; dose was defined at 0.6mg/kg with an option to increase or decrease per protocol

The majority of participants have elected to continue on Open Label Extension (OLE) Study

Metabolic decompensation events (MDEs) are serious, clinically significant events in organic acidemias

Presentation of MDEs in PA and MMA

- PA & MMA are characterized by intermittent life-threatening **MDEs**
- Patients with PA & MMA commonly present with an MDE soon after birth
- MDEs are a major contributor to mortality and long-term irreversible sequelae, such as brain damage

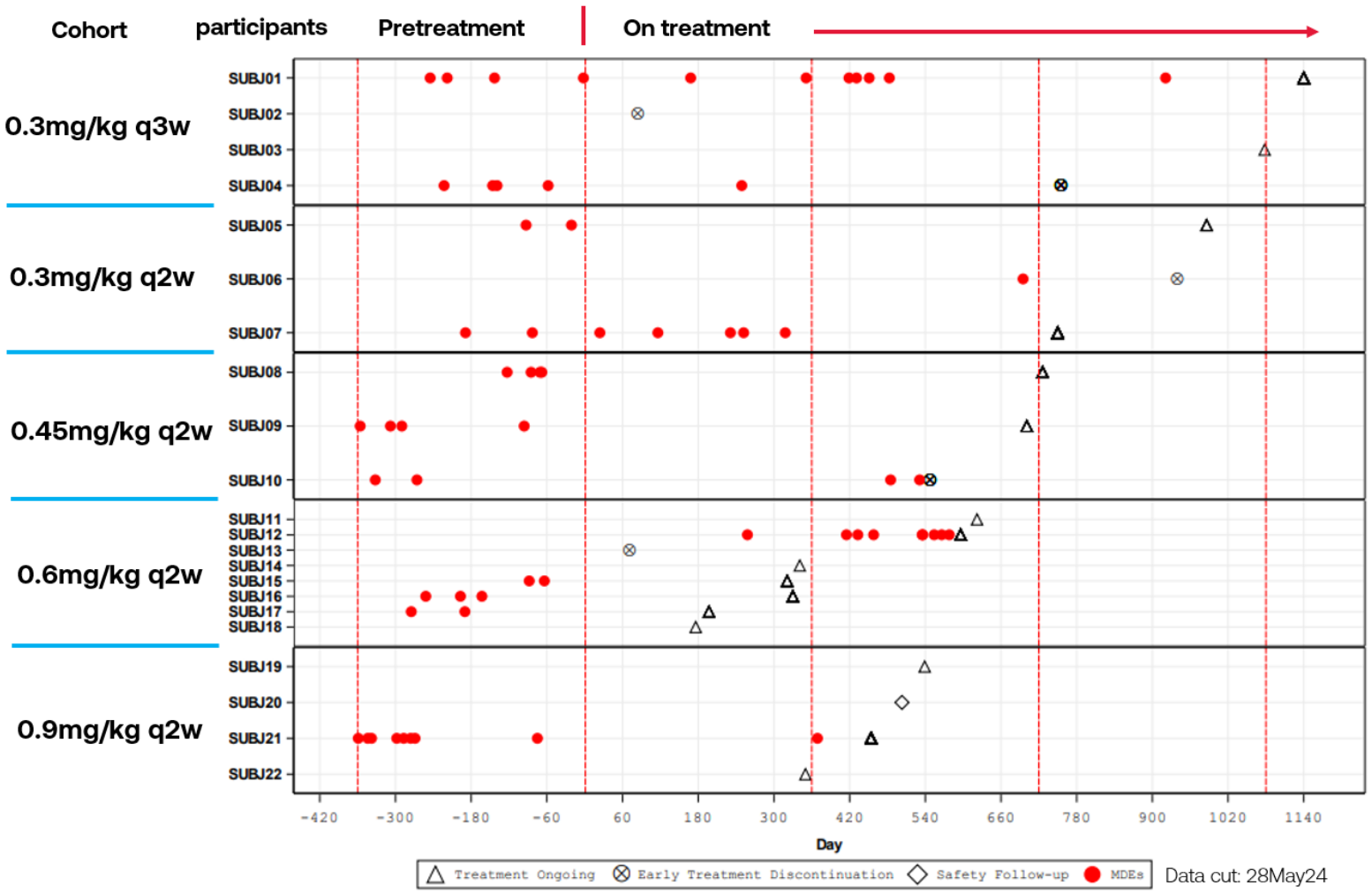
Identification and measurement of MDEs

MDEs can be objectively identified in a patient with clinical deterioration and:

- Signs or symptoms, including vomiting, anorexia, lethargy, or seizure
- Metabolic acidosis (pH <7.35)and in many cases high ammonia
- Needs acute medical care (ER or hospitalization)

- **Regulators have provided initial support for MDE as a clinically meaningful endpoint measure for therapeutic trials in patients with Propionic Acidemia**
- **Discussions with key regulators for MMA are on-going**

Summary of metabolic decompensation events (MDEs)



Data cut: 28May24

Relative risk for MDE among patients with prior MDE (95% CI)

Overall: 0.27 (0.101, 0.711)

Q2W: 0.19 (0.046, 0.808)

PA: relative MDE risk reduction improves and continues to show benefit

MDE	Data as of 25 Aug 2023	Data as of 24 May 2024
Overall RR (95% CI)	**0.29** (0.106, 0.813)	**0.27** (0.101, 0.711)
Q2W Dosing RR (95% CI)	**0.20** (0.035, 1.134)	**0.19** (0.046, 0.808)

PA: Safety

Generally well-tolerated to date

No dose limiting toxicities

Five cases of drug related serious adverse events reported in two participants (Vascular device (VD) infection Grade 2, VD infection Grade 3, Infusion site erythema Grade 2, and two Pancreatitis Grade 3)

Mild to moderate infusion related reactions were reported in <10% of doses administered

PA (mRNA-3927) summary and next steps

Clinical Results and Experience

- Early results suggest potential decreases in annualized MDE frequency and PA-related hospitalizations compared to pre-treatment
- Cumulative treatment duration of over 31.3 patient years
- Open label extension study: Majority of patients have elected to continue on open label extension study

Safety

- Generally well-tolerated to date with no events meeting protocol-defined dose-limiting toxicity criteria

Next steps

- Moderna began generating registrational trial data in 2024

Medical and scientific presentations

ASGCT 2023

https://s29.q4cdn.com/435878511/files/doc_presentations/2023/May/18/mrna-3927-pa-p101-ia-oral_asgct2023_final.pdf

2022 R&D Day

https://investors.modernatx.com/events-and-presentations/events/event-details/2022/Annual-RD-Day-2022/default.aspx

2024 NORD (patient experience)

https://s29.q4cdn.com/435878511/files/doc_presentations/2024/Oct/20/NORD_PA_Trial_Interviews_Poster_Final_v1_23SEP2024.pdf

2024 NORD (disease burden)

https://s29.q4cdn.com/435878511/files/doc_presentations/2024/Oct/20/NORD-Summit-24-Moderna-092524b_poster-7.pdf

Forward-looking statement

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding Moderna's clinical studies; encouraging early signs of potential clinical benefit for mRNA-3927; potential market size; and Moderna's engagement with global regulators. In some cases, forward-looking statements can be identified by terminology such as “may,” “should,” “expects,” “intends,” “plans,” “aims,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continue,” or the negative of these terms or other comparable terminology, although not all forward -looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties and other factors, many of which are beyond Moderna’s control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties and other factors include those described in Moderna’s most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna’s current expectations and speak only as of the date referenced on the first page.