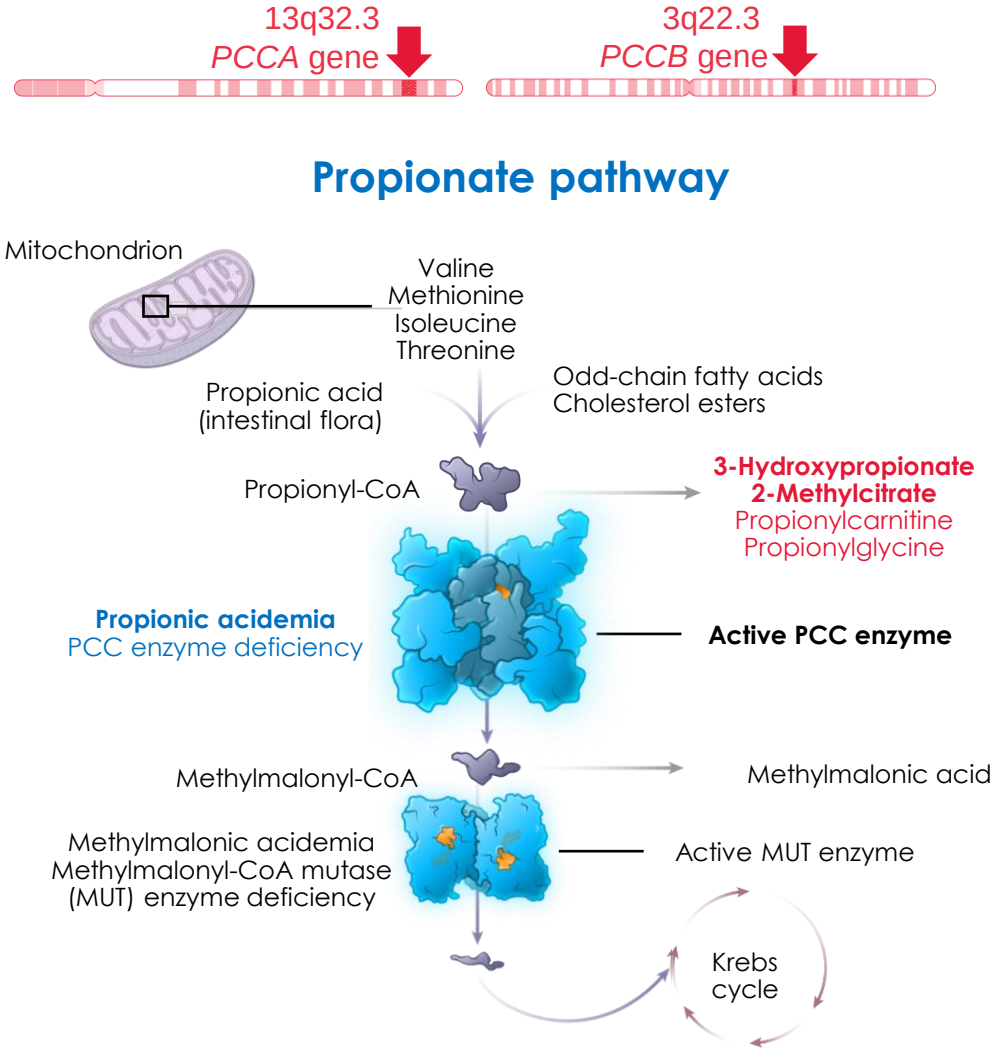
Propionic acidemia (PA) (mRNA-3927)

Last updated: September 13, 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
	Propionic acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic acidemia (MMA)	mRNA-3705						Worldwide
Rare disease intracellular therapeutics	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

Propionic Acidemia (PA) Is a Rare Inherited Metabolic Disorder

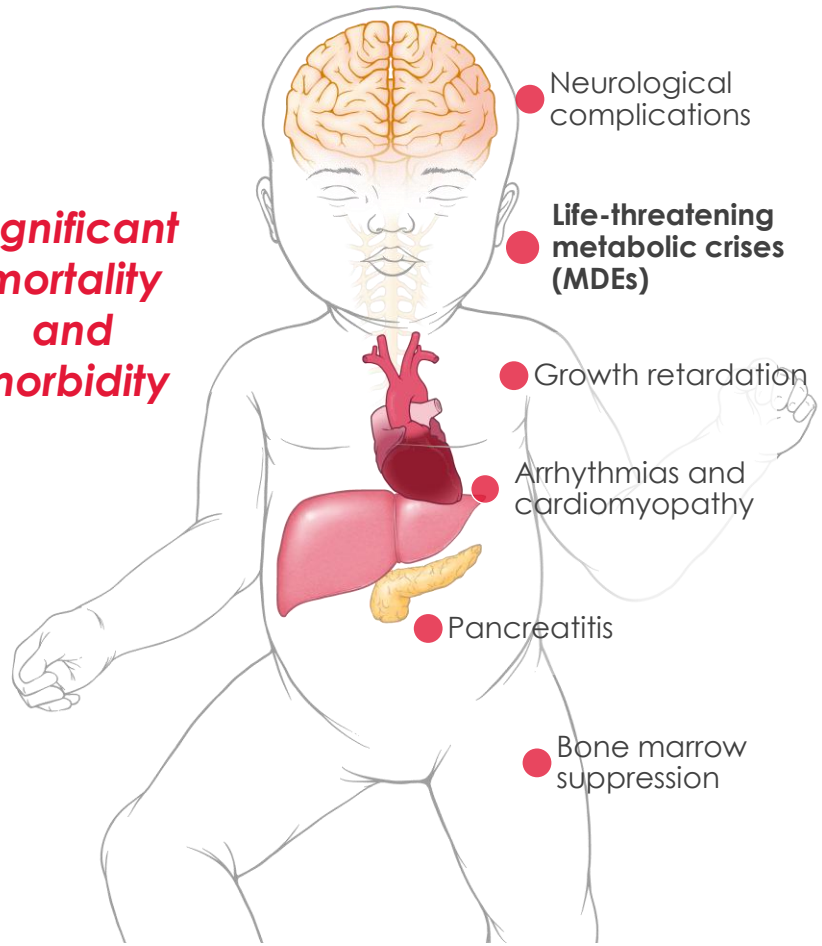
- **Rare "intoxication-type" organic acidemia**
  - Global birth prevalence estimates: 0.29–4.24 per 100,000 newborns[1]
- **Caused by pathogenic variants in *PCCA* or *PCCB* genes:**
  - Deficiency of the mitochondrial enzyme propionyl-CoA carboxylase (PCC), an heterododecamer made up of alpha (PCCA) 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



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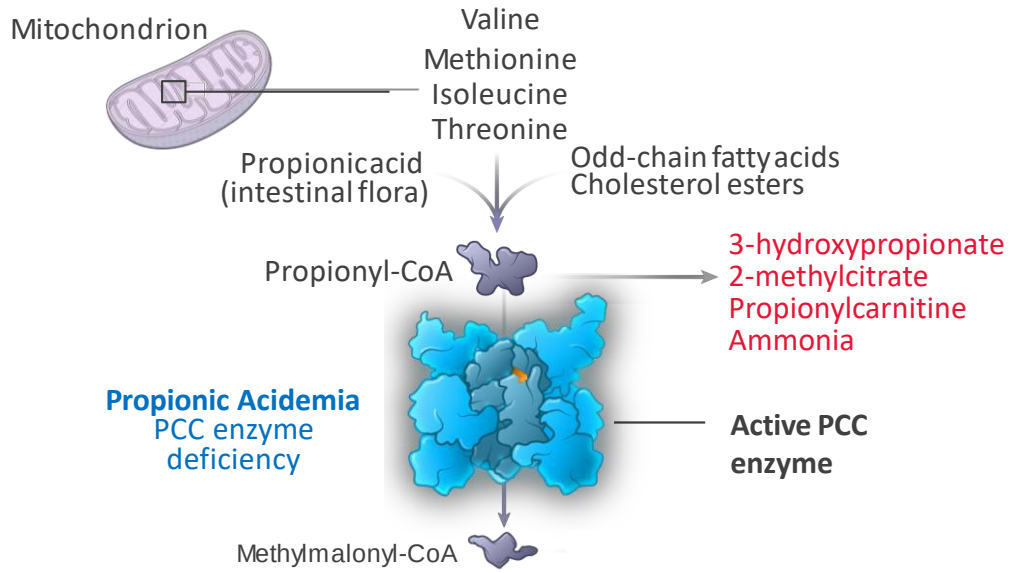
PA therapy (mRNA-3927) encodes for an intracellular enzyme

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

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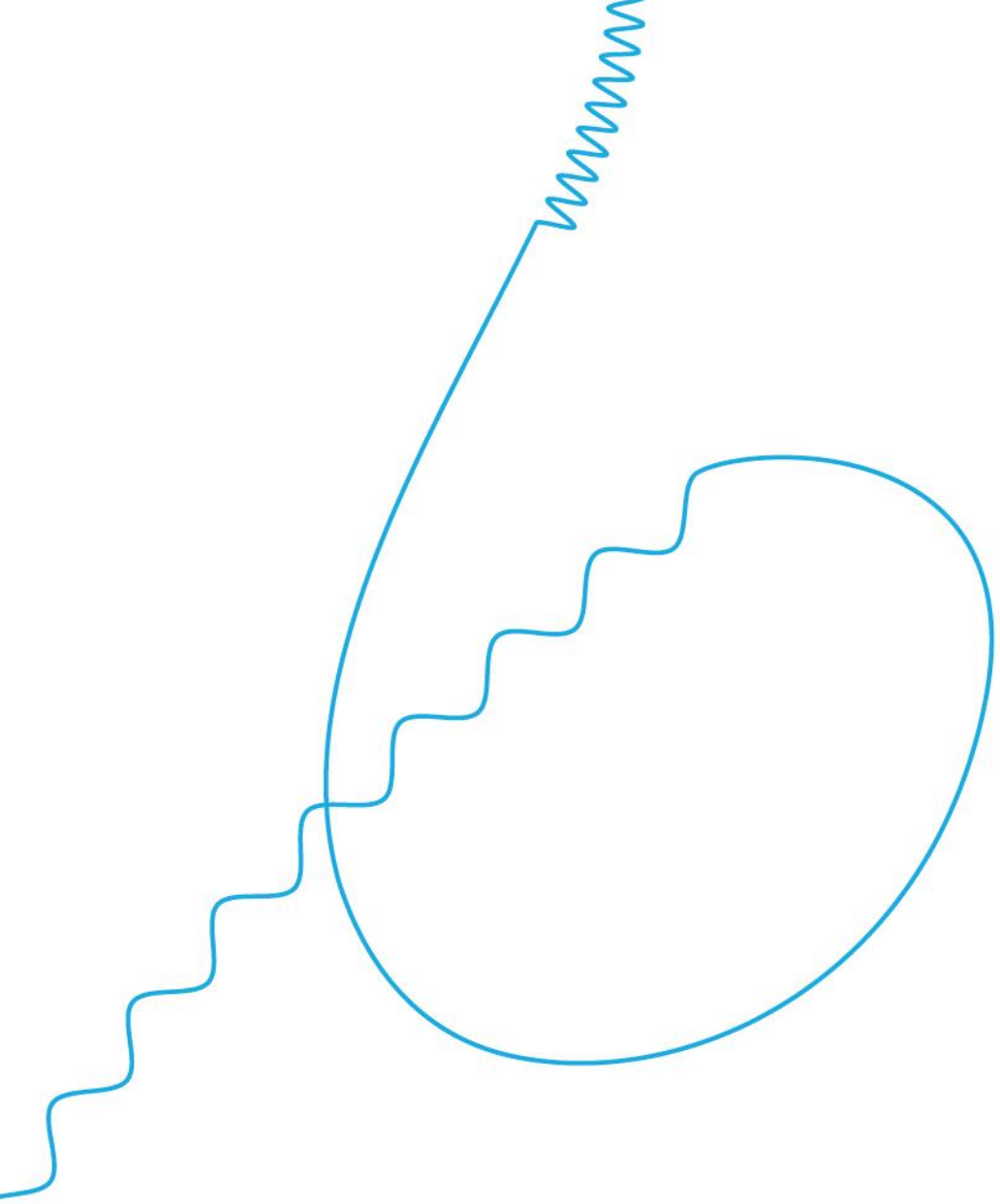

R&D Day 2023 update

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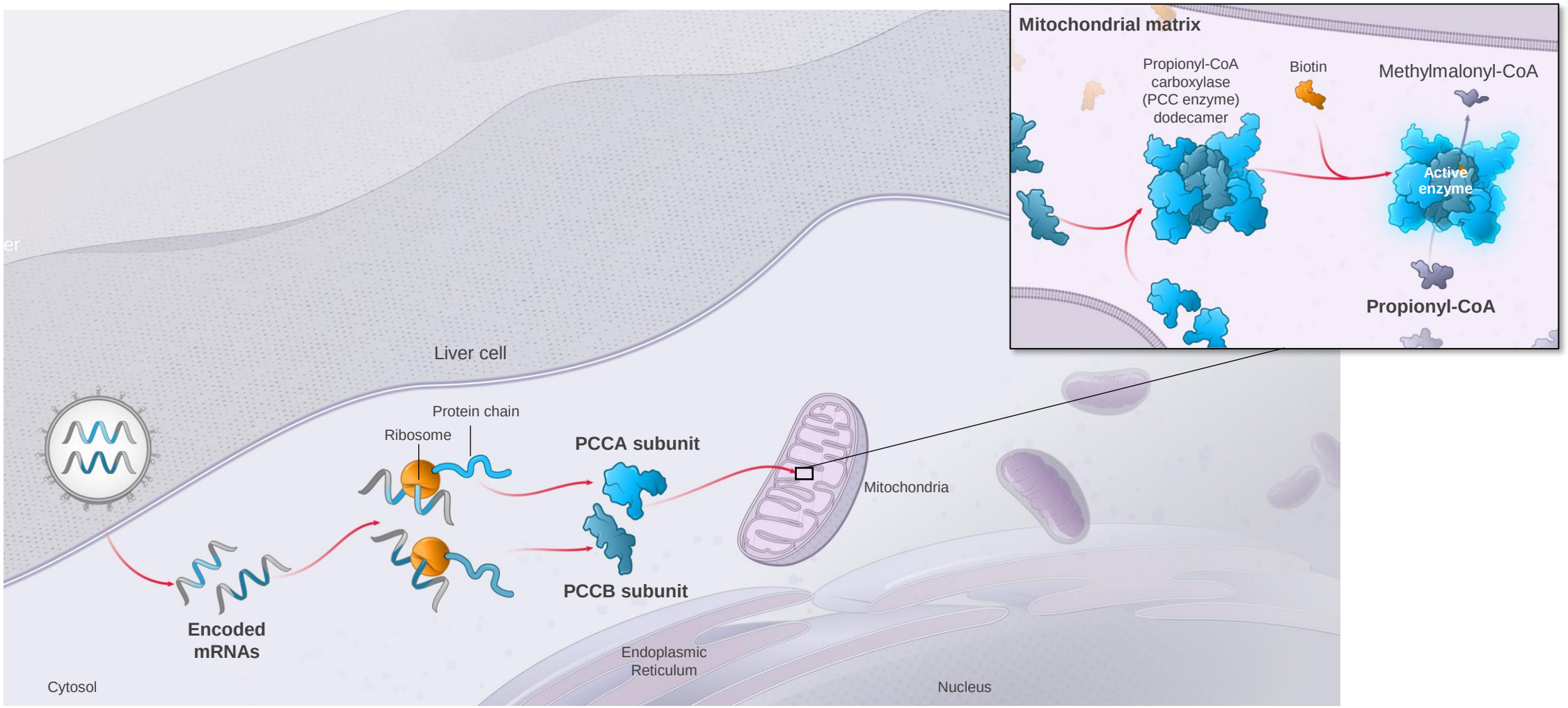
mRNA-3927 encodes for PCCA and PCCB subunit proteins to form an active PCC enzyme



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

First study testing an mRNA therapeutic for intracellular protein replacement

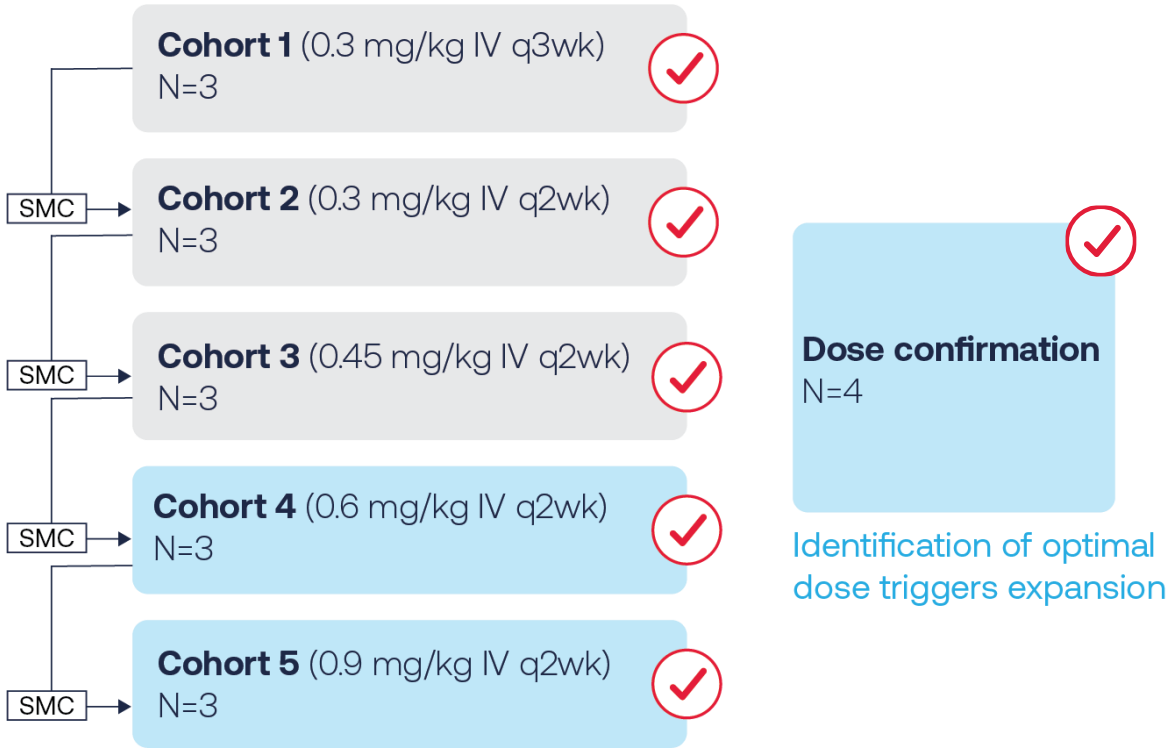
Primary endpoints: Safety and PK/PD

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)



Overall Phase 1/ 2 clinical experience

As of August 25, 2023, twenty participants have been dosed

- Twelve participants have >1 year of dosing
- 19.1 cumulative patient-years of experience on study drug
- Longest duration of treatment is 2.4 years and median duration 0.9 years
- Over 433 intravenous doses administered
- Study is ongoing; independent safety monitoring committee approved moving to fifth cohort (0.9 mg/kg)

- The majority of participants have elected to continue on Open Label Extension (OLE) Study
- Generally well-tolerated to date
- No dose limiting toxicities
- Three cases of drug related serious adverse events reported in two participants (Vascular device infection Grade 2, Infusion site erythema Grade 2, and Pancreatitis Grade 3[1])
- Mild to moderate infusion related reactions were reported in <10% of doses administered

1 Patient had a history of recurrent pancreatitis prior to enrollment

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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**

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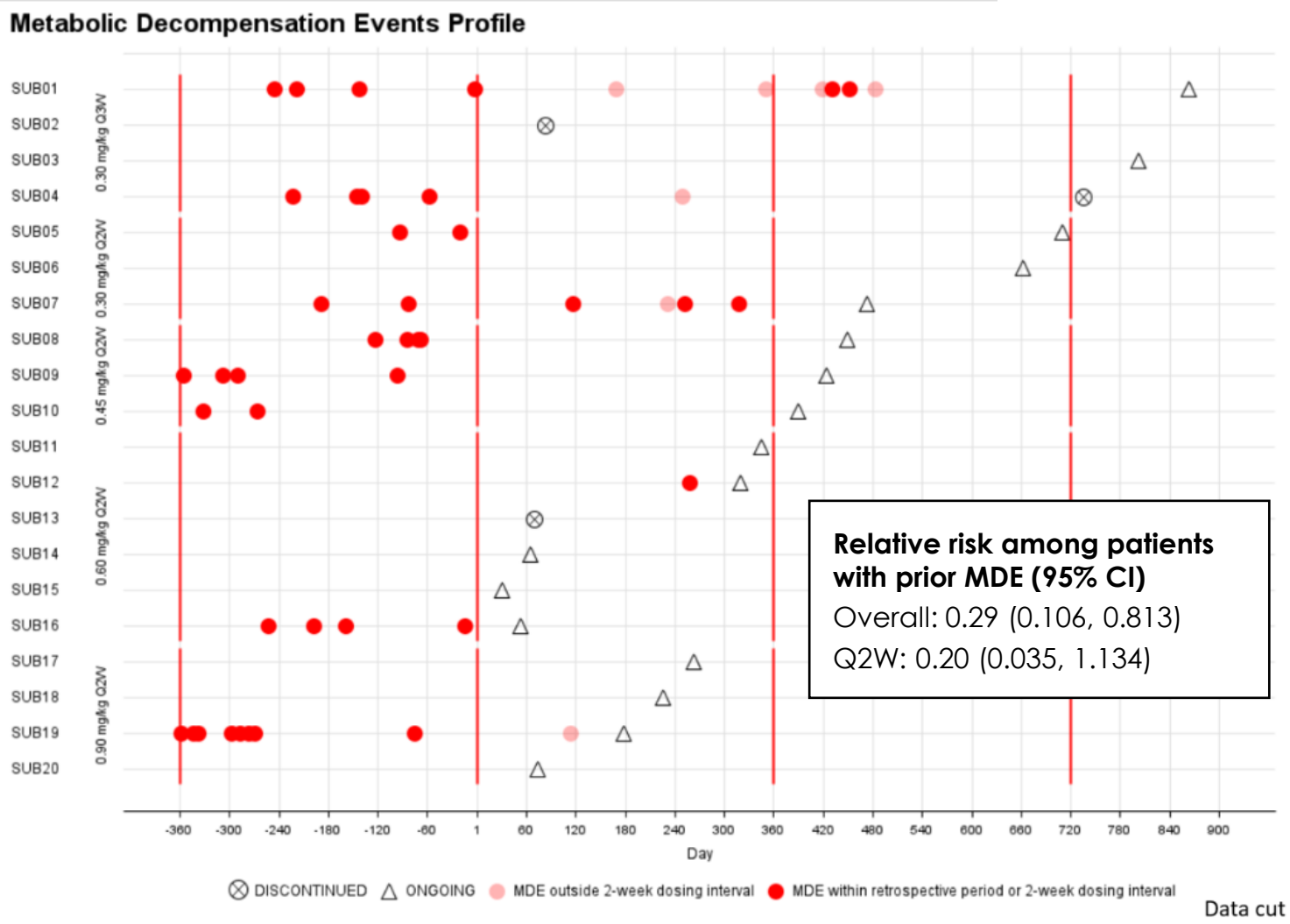
Summary of metabolic decompensation events (MDEs)



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

Overall: 0.29 (0.106, 0.813)

Q2W: 0.20 (0.035, 1.134)

Data cut 25 Aug 2023

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Summary

- **Expanding clinical experience:** Cumulative treatment duration of over 19.1 patient years
- **Safety:** Generally well-tolerated to date with no events meeting protocol-defined dose-limiting toxicity criteria
- **Clinical endpoints:** Early results suggest potential decreases in annualized MDE frequency and PA-related hospitalizations compared to pre-treatment
- **Open label extension study:** Majority of patients have elected to continue on open label extension study
- **Next steps:** Continue study enrollment and identify an optimal dose while engaging with global regulators on a path to registration

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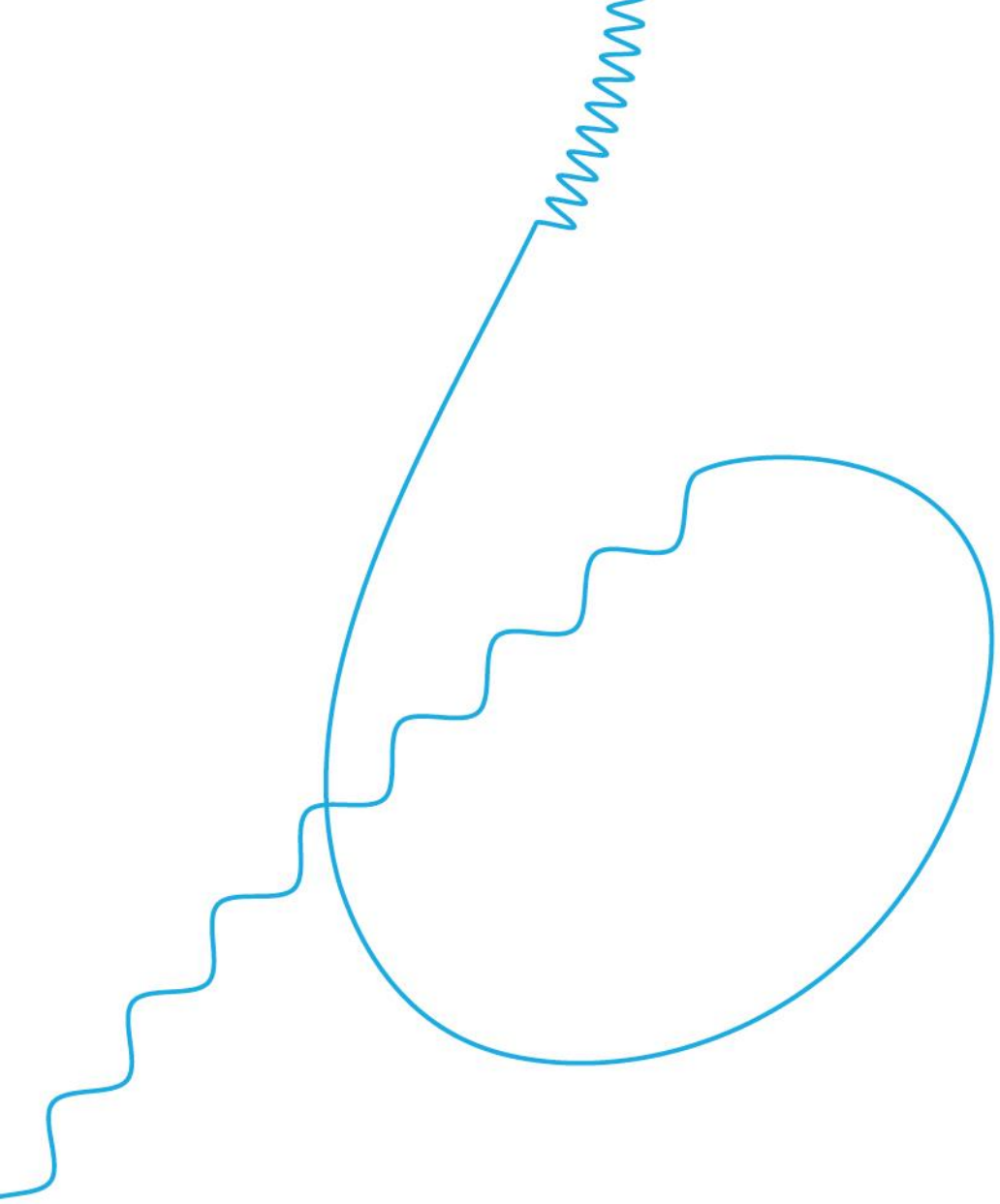

ASGCT 2023 update

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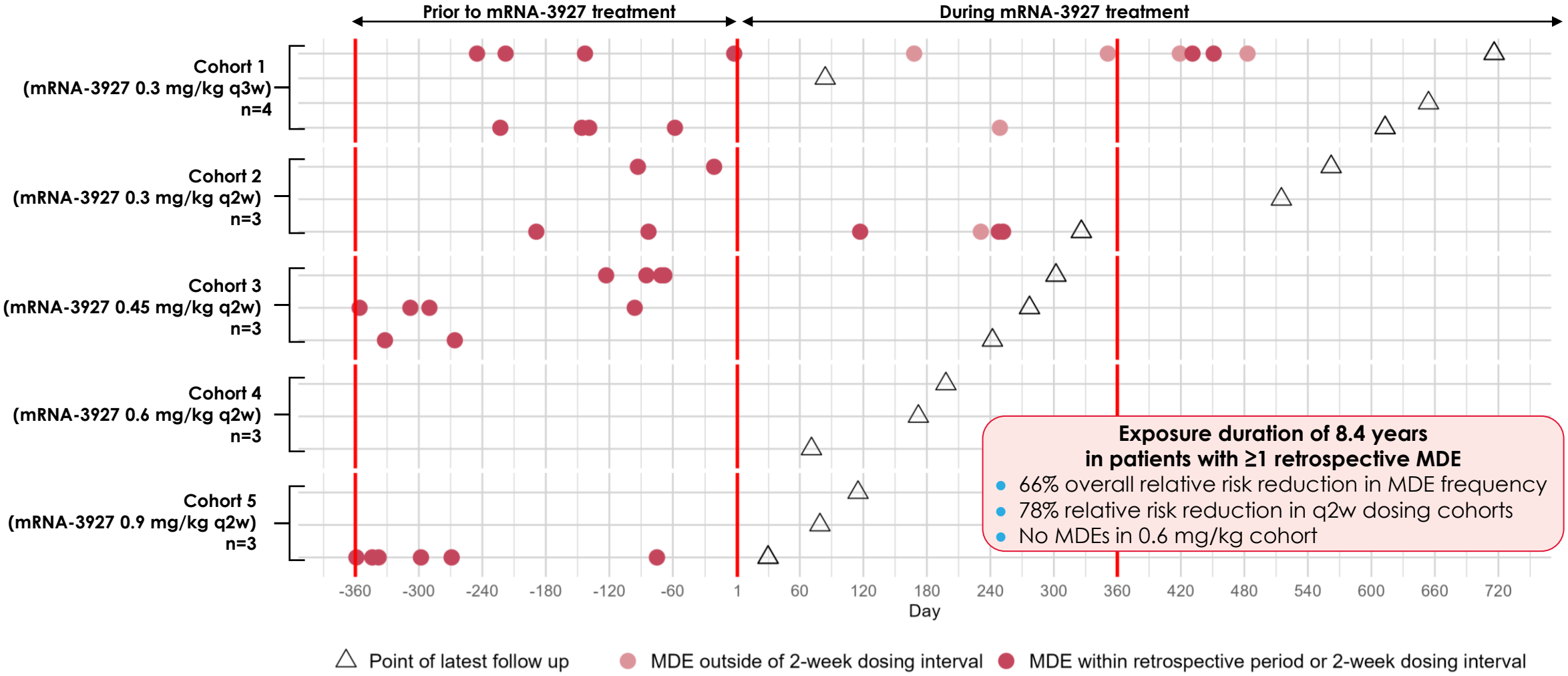
ASGCT 2023: Summary of Metabolic Decompensations Events (MDEs)



Includes mRNA-3927-P101 and extension studies.
The generalized linear mixed models for MDE number and duration includes period, dosing frequency, and period-by-dosing frequency as independent variables, duration of observation as an offset and a random effect to consider the repeated measurements within a patient.
q2w, every 2 weeks; q3w, every 3 weeks; MDE, metabolic decompensation event.

ASGCT 2023: Conclusions

- **This is the first clinical trial reporting results of an mRNA therapeutic for intracellular protein replacement**
- **16 patients dosed**
  - >280 intravenous doses of mRNA-3927
  - 5 patients received >1 year of dosing
  - More than 13 patient-years' experience on drug
  - All eligible participants continue to opt-in to the open-label expansion
- **To date, mRNA-3927 has been well-tolerated in patients with PA at the doses administered, with no dose-limiting toxicities**
- **Results show encouraging early signs of potential clinical benefit with mRNA-3927**
  - Reductions in the number of metabolic decompensation events were observed after the start of mRNA-3927 treatment in patients who reported them in the 12 months prior to dosing
- **The study is ongoing**
  - Next steps include confirming the optimal therapeutic dose and evaluating it in additional patients, including infants

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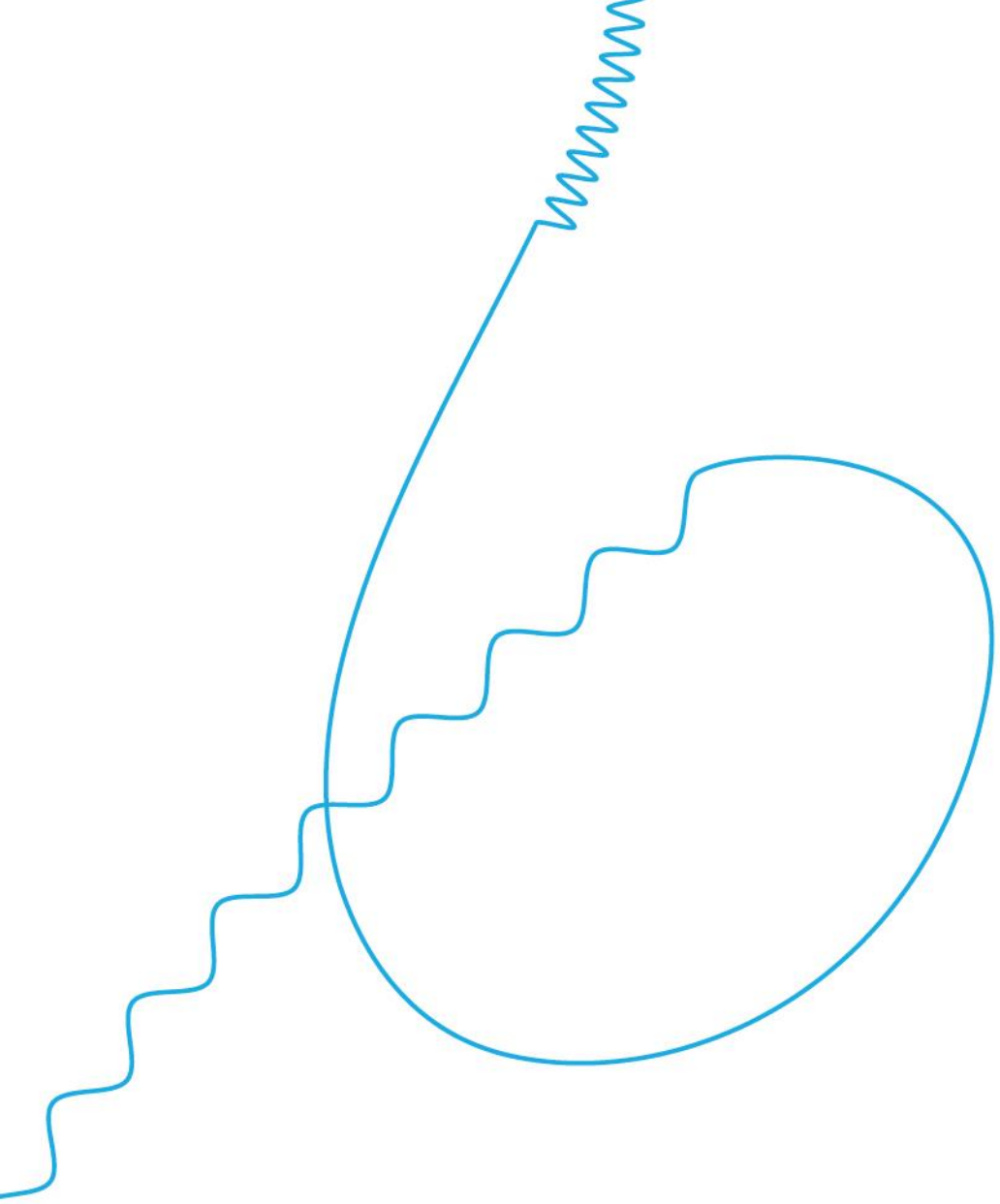

R&D Day 2022 Update: Ongoing Phase 1/2 study – Update from first three cohorts

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mRNA-3927: Summary of demographics and baseline characteristics

	Cohort 1 0.3 mg/kg q3W (n=4)	Cohort 2 0.3 mg/kg q2W (n=3)	Cohort 3 0.45 mg/kg q2W (n=3)	All (n=10)
Age at enrollment, median (years)	15.42	2.33	3.75	6.71
Min, Max	5.2 , 26.8	1.5 , 8.3	1.6, 15.3	1.5, 26.8
Age at disease onset, median (months)	0.0	0.0	0.0	0.0
Min, Max	0, 1	0, 0	0, 1	0, 1
Sex, n				
Male	2	0	2	4
Female	2	3	1	6
Race, n				
White	1	2	1	4
Black or African American	0	0	1	1
Asian	3	0	1	4
Other (Black African)	0	1	0	1
Ethnicity, n				
Not Hispanic or Latino	4	3	3	10
Weight				
Weight at baseline, median (kg)	44.40	15.80	18.00	23.05
Min, Max	21.6. 66.5	10.6, 24.8	11.2, 42.7	10.6, 66.5
Genotype				
PCCA	2	1	2	5
PCCB	2	2	1	5

Overall Phase 1/ 2 clinical experience – cohorts 1-3

- Ten participants dosed
- Three participants have >1 year of dosing
- 6 patient-years of experience on drug
- Over 120 intravenous doses administered
- All participants eligible have decided to continue on Open Label Extension (OLE) Study

Safety: Overall summary

- Generally well-tolerated to date
- No Dose Limiting Toxicities
- No Drug Related Serious Adverse Events
- No Discontinuations due to safety
- Only drug related adverse events were mild to moderate infusion related reactions (<10% of doses)

Safety: Summary of all adverse events measured

Adverse events (AEs) collected in the trial consist of treatment emergent adverse events (any AE reported after the start of dosing) and drug related AEs

	Cohort 1 0.30 mg/kg Q3W (N=4)	Cohort 2 0.30 mg/kg Q2W (N=3)	Cohort 3 0.45 mg/kg Q2W (N=3)	Total (N=10)
Treatment-emergent adverse events[1]	**3 (75.0)**	**3 (100)**	**3 (100)**	**9 (90.0)**
Dose Limiting Toxicity	0	0	0	**0**
AEs leading to study discontinuation	0	0	0	**0**
Serious adverse events[2]	2 (50.0)	2 (66.7)	1 (33.3)	**5 (50.0)**
Drug-related adverse events	**2 (50.0)**	**0**	**0**	**2 (20.0)**
Drug-related Serious Adverse Events	0	0	0	**0**

[1] Treatment-emergent adverse events are defined as AEs reported on or after the date that the intervention began

[2] Serious adverse events are defined as AEs including those leading to hospitalization, or disability, or are life-threatening or result in death, or deemed by the investigator as medically important, and include congenital anomaly or birth defect

Safety: Summary of serious adverse events

No drug-related SAEs; several SAEs due to underlying disease

	Cohort 1 0.30 mg/kg Q3W (N=4)	Cohort 2 0.30 mg/kg Q2W (N=3)	Cohort 3 0.45 mg/kg Q2W (N=3)	Total (N=10)
All Serious Adverse Events	**2 (50.0)**	**2 (66.7)**	**1 (33.3)**	**5 (50.0)**
Dyskinesia	0	1 (33.3)	0	1 (10.0)
Gastroenteritis viral	0	1 (33.3)	0	1 (10.0)
Mastoiditis	1 (25.0)	0	0	1 (10.0)
Parainfluenza virus infection	0	1 (33.3)	0	1 (10.0)
Poor venous access	0	0	1 (33.3)	1 (10.0)
Staphylococcal sepsis	1 (25.0)	0	0	1 (10.0)
Serious AEs related to underlying disease				
Metabolic disorder	1 (25.0)	0	0	1 (10.0)
Vomiting	1 (25.0)	0	1 (33.3)	2 (20.0)
Depression	1 (25.0)	0	0	1 (10.0)
Drug-related Serious adverse events	**0**	**0**	**0**	**0**

Treatment-emergent adverse events are defined as AEs reported on or after the date that the intervention began
All serious adverse events in the study were treatment-emergent adverse events

Safety: Summary of drug-related adverse events

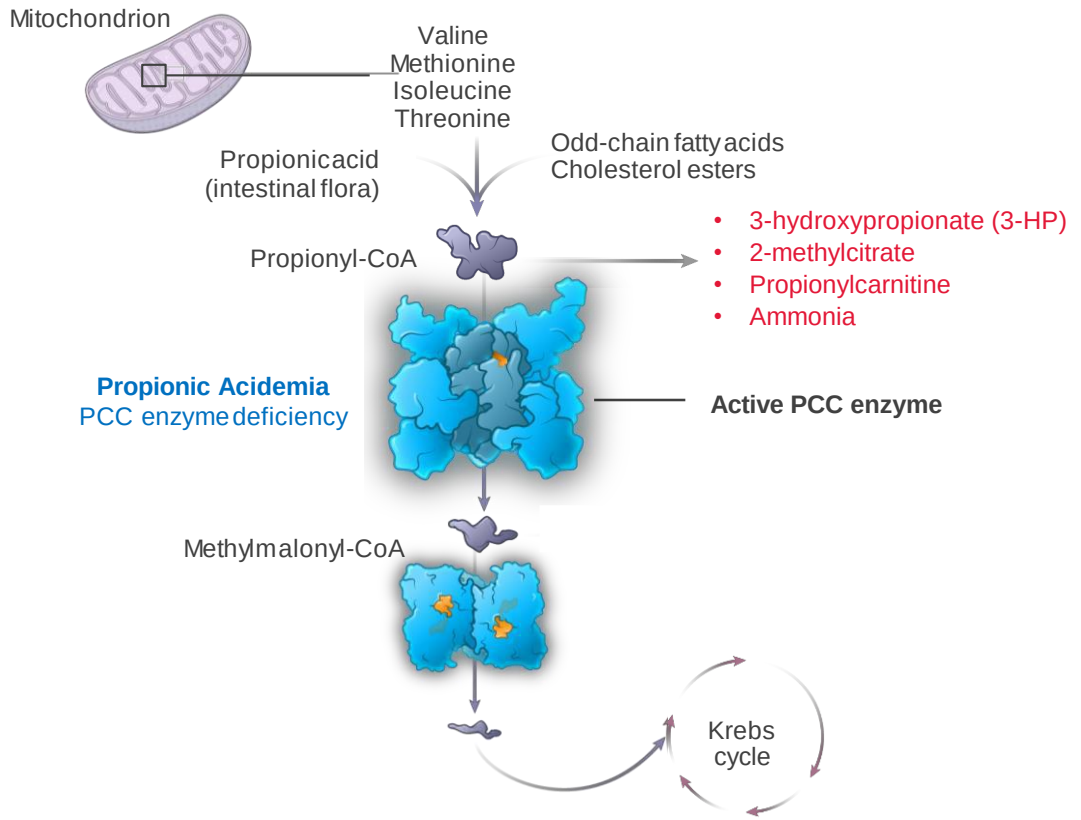
All drug related AEs were mild to moderate infusion related reactions (IRRs) that occurred in cohort 1 only

	Cohort 1 0.30 mg/kg Q3W (N=4)	Cohort 2 0.30 mg/kg Q2W (N=3)	Cohort 3 0.45 mg/kg Q2W (N=3)	Total (N=10)
Drug-related adverse events	**2 (50.0)**	**0**	**0**	**2 (20.0)**
By CTCAE grade				
Grade 1	2 (50.0)	0	0	**2 (20.0)**
Grade 2	1 (25.0)	0	0	**1 (10.0)**
Grade 3 or above	0	0	0	**0**
Serious adverse events	0	0	0	**0**
Total Number of Doses Given	61	49	12	**122**
Number of doses with IRRs	11 (18.0)	0	0	**11 (9.0)**

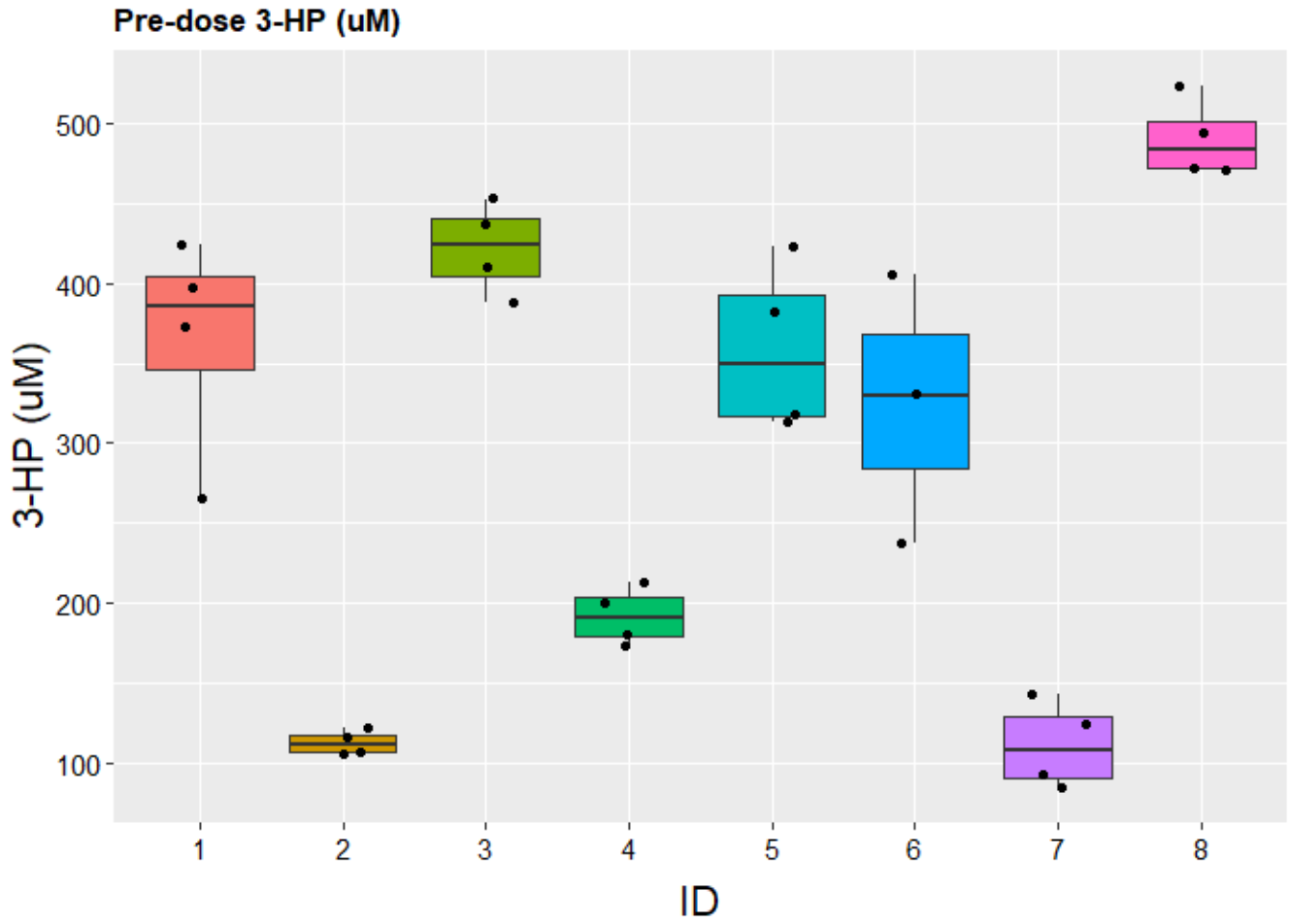
IRRs: Infusion-related reactions, defined as a drug-related AEs occurring within 24 hours of the start of a dose

Biomarkers to evaluate PK/PD of mRNA-3927

- While **several biomarkers have been described**, their pattern in individual patients over time and association with clinical events has not been thoroughly studied
- **No clinically validated** biomarkers
- We **explored 3-Hydroxypropionate (3-HP) as a potential biomarker**



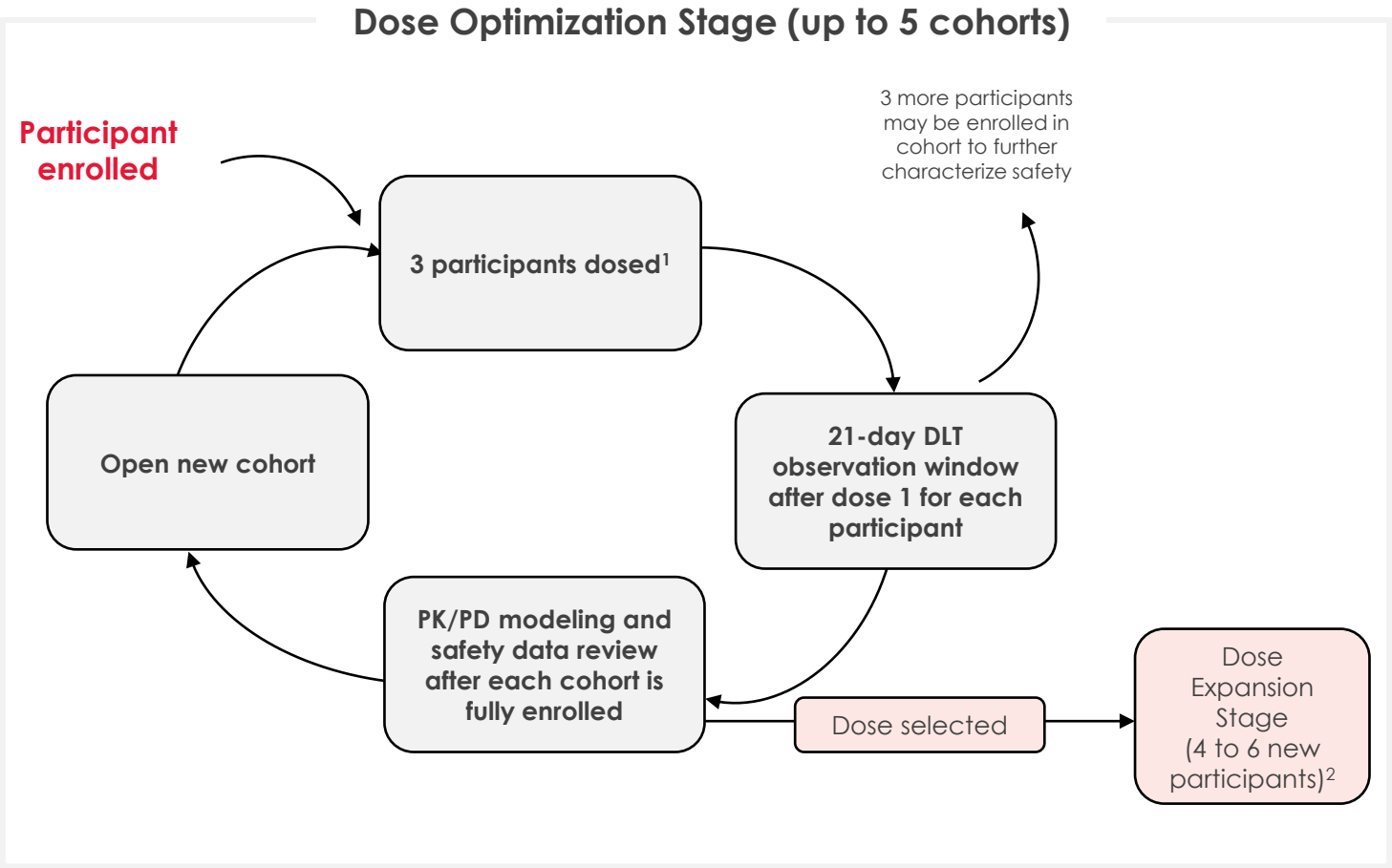
Baseline 3-HP biomarker levels highly variable across patients



PA genotype	Patient ID
PCCA	1, 5, 8
PCCB	2, 3, 4, 6, 7

- Each patient in the trial had four 3-HP values measured from blood draws taken before treatment
- Pre-treatment 3-HP values are highly variable between patients and within patients

Adaptive study design to identify optimal dose level and frequency



- Shorten interval from 3 weeks to 2 weeks (Cohort 2)
- Increased dose to 0.45 mg/kg (Cohort 3)
- Increased dose to 0.6 mg/kg (Cohort 4) expected to begin dosing shortly

DLT = dose-limiting toxicity; PD = pharmacodynamic(s); PK – pharmacokinetic(s)
1. The first 2 participants will be ≥ 8 years of age
2. In the dose expansion stage, a minimum of 2 participants with each PA subtype will be enrolled

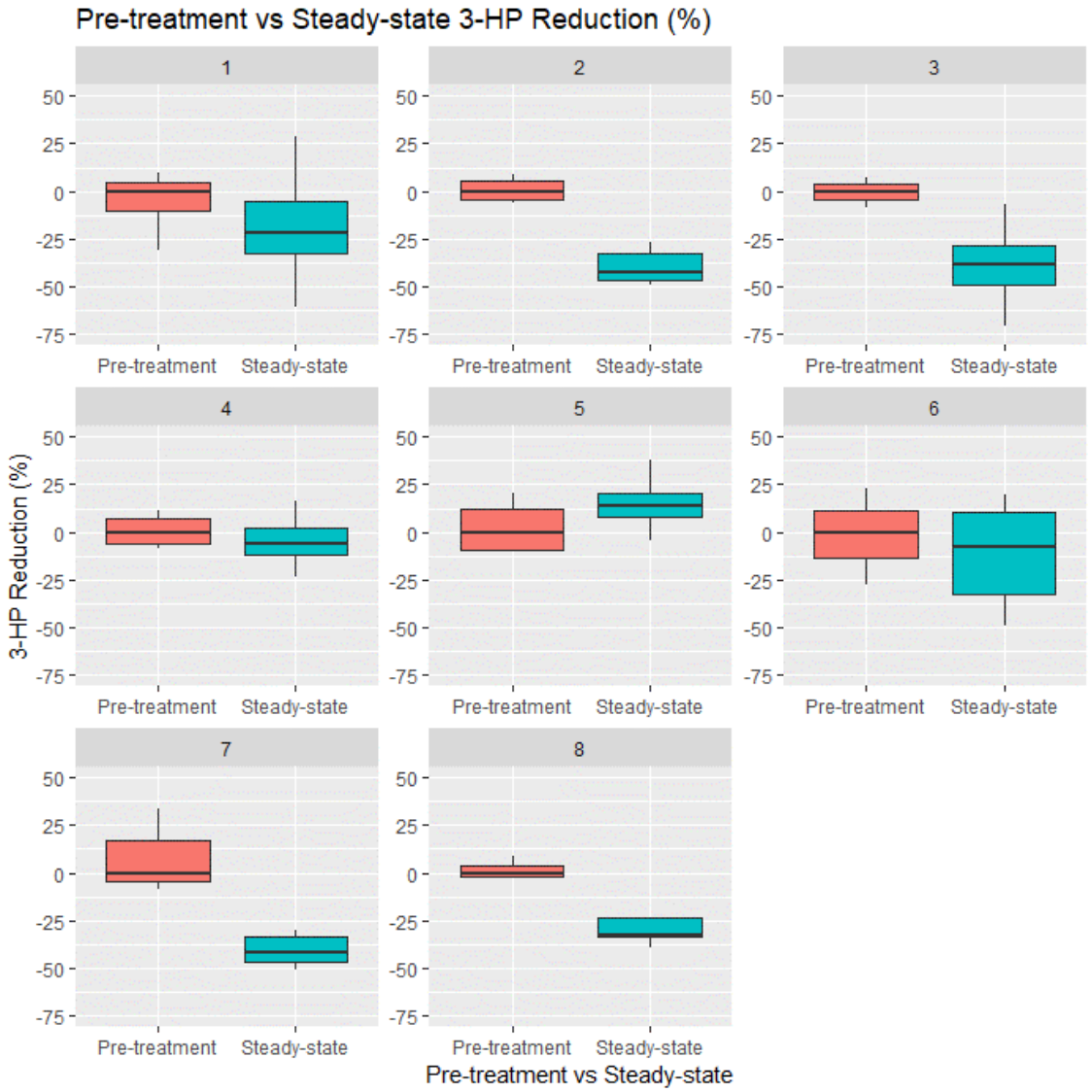
Significant reduction in 3-HP biomarker observed

- 7/8 patients showed a numerical reduction in 3-HP

Cohort 1 (0.3 mg/kg Q3W)

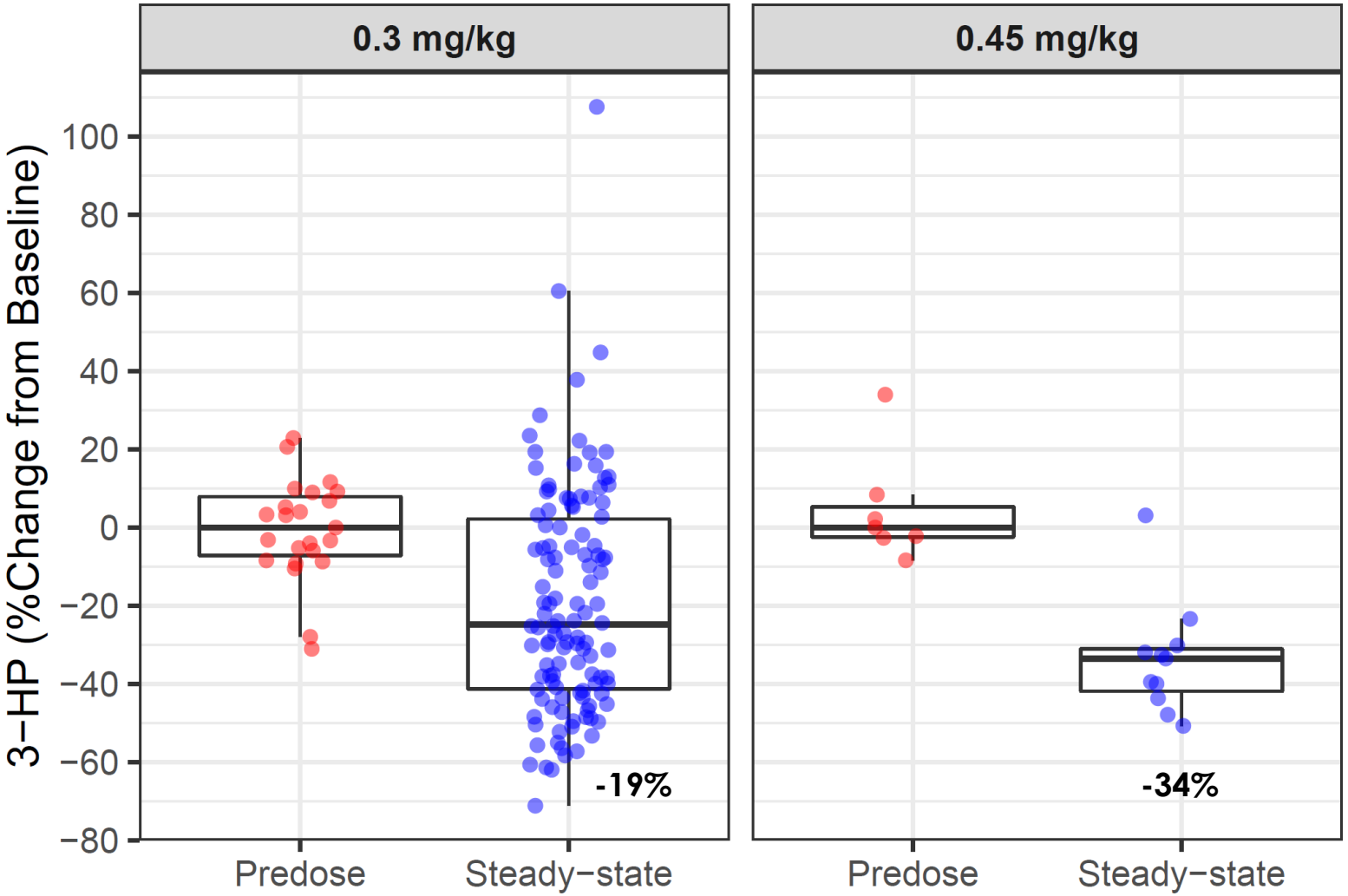
Cohort 2 (0.3 mg/kg Q2W)

Cohort 3 (0.45 mg/kg Q2W)



Steady-state = 3-HP measurements taken at all visits post 3rd dose

Encouraging trend in 3-HP biomarker



- Patients showed numerically lower 3-HP levels on treatment
- Trend suggestive of potential dose response with a greater decline from baseline at 0.45 mg/kg

Baseline= 3-HP measurements collected from pretreatment visits (N=4 visits/measurements per subject, prior to first dose);
Steady-state = 3-HP measurements taken at all visits post 3rd dose

Metabolic decompensation events are a potential primary endpoint

Protocol definition of MDE

- Exacerbation of symptoms of propionic acidemia: Persistent vomiting, anorexia/failure to feed, lethargy or increased seizure activity

and…

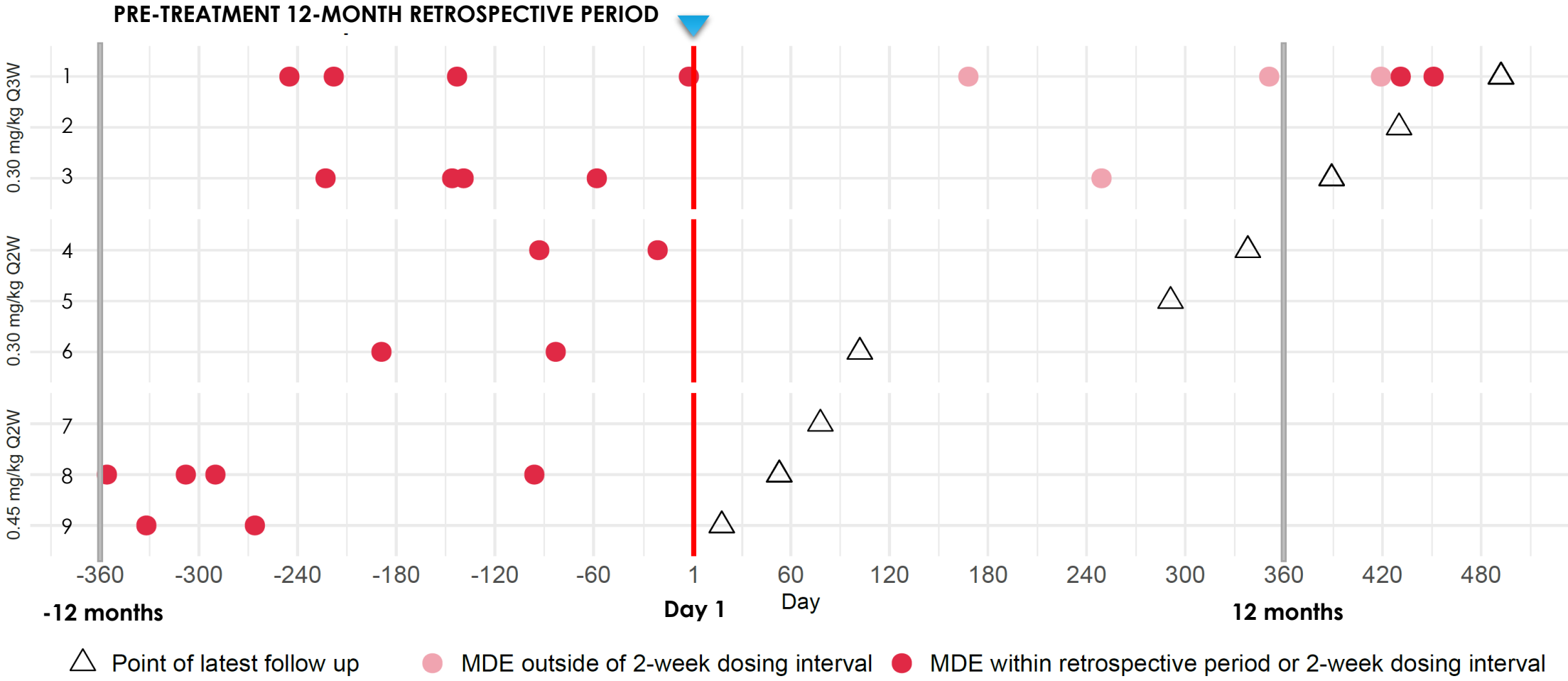
- Requiring emergency medicalcare (ER or hospitalization admission)

and at least one of:

- Metabolic acidosis (pH < 7.35) with high anion gap, or imminent metabolic acidosis with high anion gap (normal pH with reduced bicarbonate and/or PaCO2)
- Acute Hyperammonemia requiring intervention

Initial discussions with regulators supportive of MDE as primary endpoint for a pivotal study

Summary of metabolic decompensation events (MDEs)



Exposure duration of 3.8 years in participants with ≥1 retrospective MDE

- 48% Relative risk reduction in MDE frequency (p-value = 0.1817)
- No MDEs in two-week dosing interval cohorts

Summary of Phase 1/2 preliminary data; study ongoing to identify optimal dose

- **Expanding clinical experience:** More than 6 patient-years of experience on drug and all participants eligible have decided to continue drug on the Open Label Extension (OLE) Study
- **Safety:** Generally well-tolerated to date with no drug-related serious adverse events, no discontinuations due to safety and only mild-to-moderate infusion related reactions (<10% of doses)
- **Encouraging early trends in 3-HP biomarkers:** Suggestive of potential dose-dependent pharmacology
- **Clinical endpoints:** Encouraging data shows decrease in the number of metabolic decompensation events (MDEs)
- **Next steps**: Continue enrolling cohort 5, dose selection for the expansion arm of the phase 1/2 study

mRNA-3927 Therapy for Propionic Acidemia: Interim Data From a Phase 1/2 Study

Stephanie Grunewald,[1] Saikat Santra,[2] Dwight Koeberl,[3] Andreas Schulze,[4] Neal Sondheimer,[4] Ayesha Ahmad,[5] **Gerald Lipshutz**,[6] Tarekegn Geber Hiwot,[7] Min Liang,[8] Lerong Li,[8] Ruchira Glaser,[8,*], Nuria Carrillo,[8] on behalf of the Paramount Trial Investigators

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- **Rare "intoxication-type" organic acidemia**

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- **Caused by pathogenic variants in *PCCA* or *PCCB* genes:**

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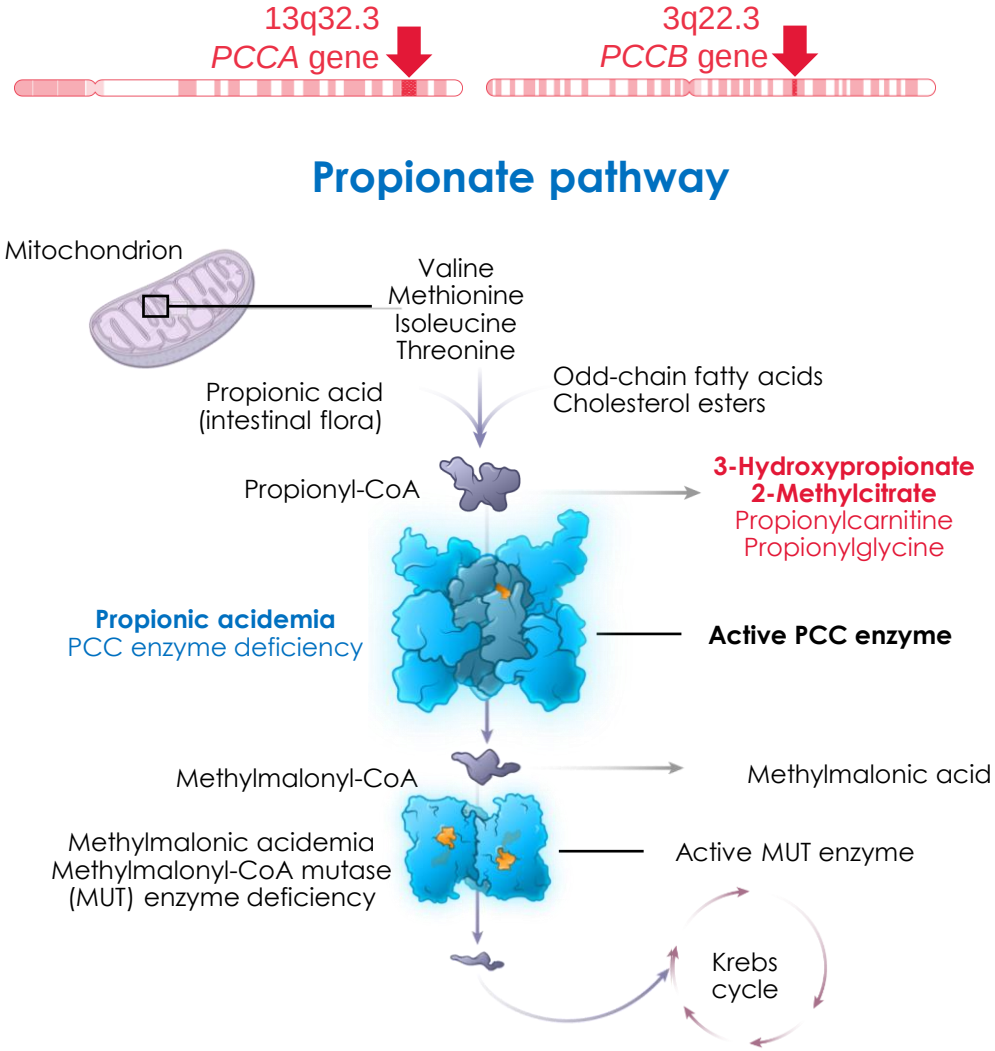


1. Almasi T, et al. *Orphanet J Rare Dis.* 2019;14:40. 2. Shchelochkov OA, et al. In: GeneReviews®. https://www.ncbi.nlm.nih.gov/books/NBK92946/. 3. Haijes HA, et al. *J Inherit Metab Dis.* 2019;42:745-761.

Clinical Characteristics and Management of PA

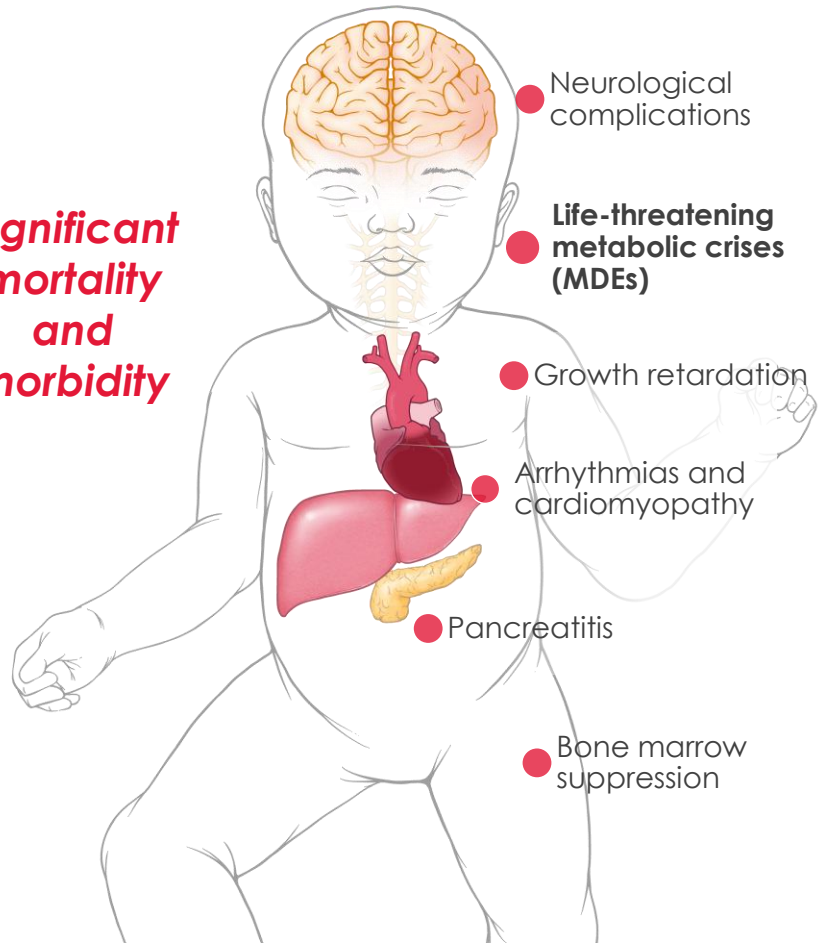
- Primarily a **pediatric disease**, with **onset typically in neonates** resulting in **significant morbidity and mortality**[1,2]
- **Characterized by recurrent, life-threatening metabolic decompensation events**[1-3]

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]

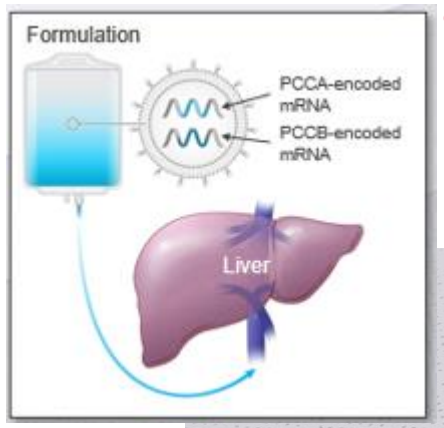
Liver transplant improves biochemical and clinical outcomes; transplant is not curative

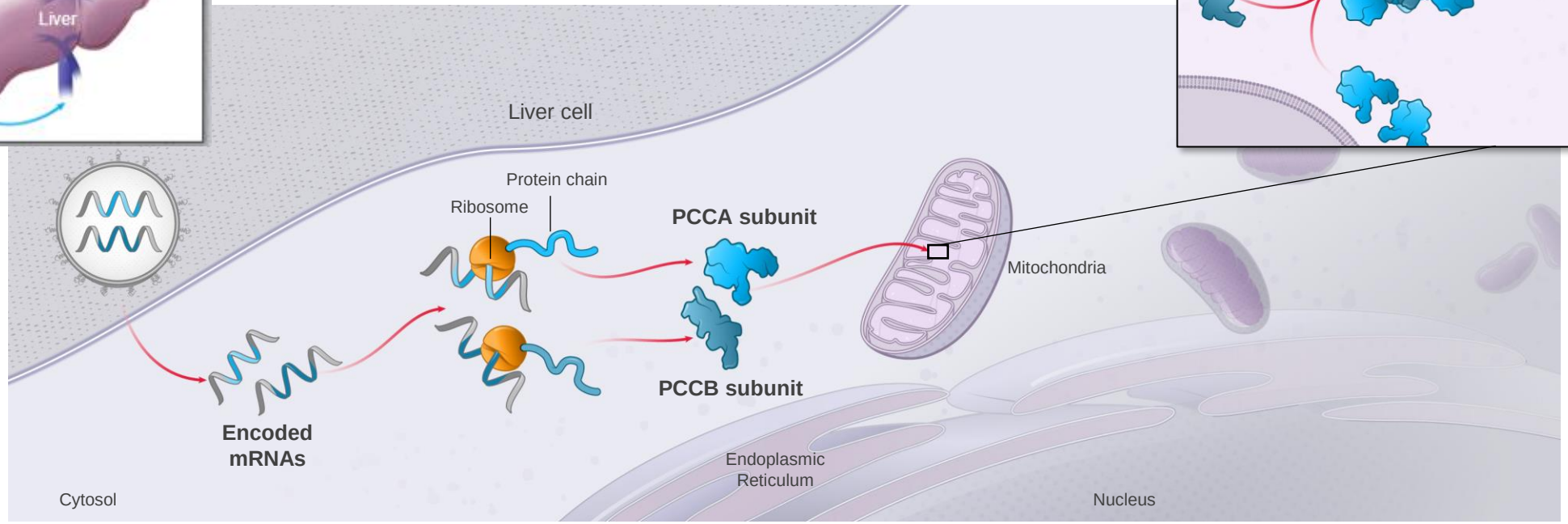


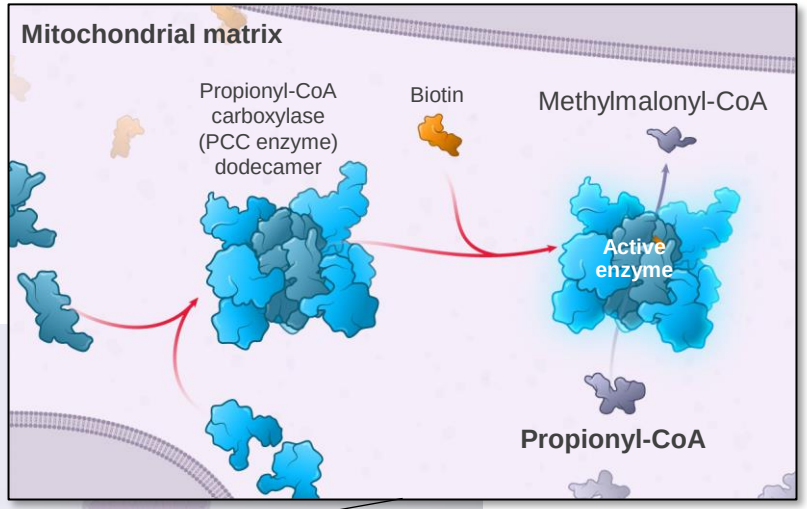
1. Shchelochkov OA, et al. In: GeneReviews®. https://www.ncbi.nlm.nih.gov/books/NBK92946/. 2. Fraser JL, et al. *Curr Opin Pediatr.* 2016;28:682-693. 3. Jurecki E, et al. *Mol Genet Metab.* 2019;126:341-354. 4. Grunert SC, et al. *J Inherit Metab Dis.* 2012;35:41-49. 5. Haijes HA, et al. *J Inherit Metab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

An Introduction to mRNA-3927

- **mRNA-3927 is a novel, IV-administered, lipid nanoparticle (LNP)-encapsulated dual mRNA therapy that encodes for PCCA and PCCB subunit proteins to restore functional PCC enzyme activity in the liver**
- **By encoding for intracellular proteins, mRNA therapy has a potential role in preventing and treating acute metabolic decompensations**



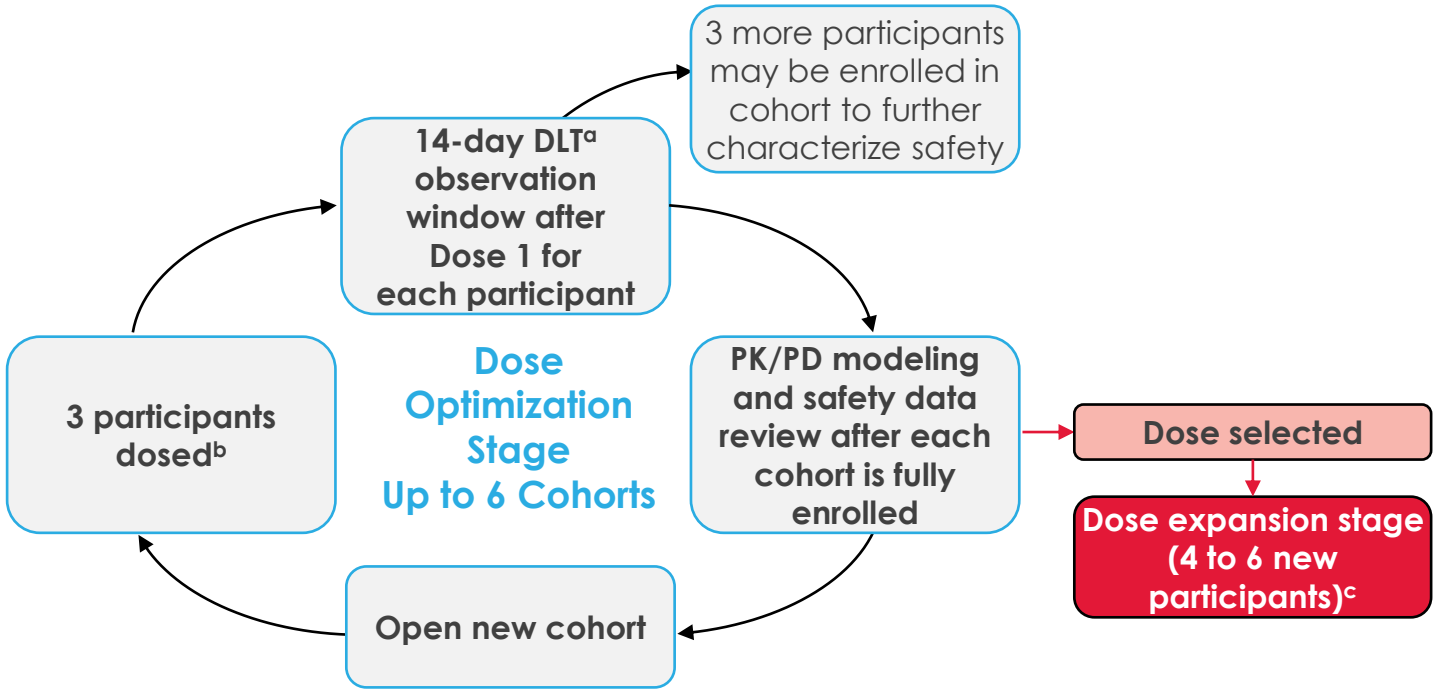




IV, intravenous.

mRNA-3927 Phase 1/2 Trial Overview

- **PARAMOUNT: A global, phase 1/2, open-label, dose optimization study to evaluate the safety, pharmacodynamics, and pharmacokinetics of mRNA-3927 in participants with PA (NCT04159103; mRNA-3927-P101)**



- **Primary endpoints:**
  - Incidence and severity of AEs, SAEs, and AEs leading to discontinuation
- **Secondary endpoints:**
  - Include changes in plasma biomarkers and PK of mRNA-3927
- **Exploratory clinical endpoints:**
  - Include metabolic decompensation events

- **Participants receive up to 10 doses of mRNA-3927, then may enter a 2-year safety follow-up period, or continue to receive mRNA-3927 in an extension study (NCT05130437)**

[a]Dose-limiting toxicities (DLTs) were defined as TEAEs that occurred during the first 14 days following administration of the first dose of mRNA-3927, and were grade ≥3 regarded as possibly or probably related to mRNA-3927. [b]The first 2 patients were to be ≥8 years of age. [c]In the dose expansion stage, a minimum of 2 patients with each PA subtype (*PCCA* or *PCCB* variant) will be enrolled.
AE, adverse event; DLT, dose-limiting toxicity; PD, pharmacodynamics; PK, pharmacokinetics; SAE, serious adverse event.

Inclusion/Exclusion Criteria for the mRNA-3729-P101 Phase 1/2 Study

Key Inclusion Criteria

- ≥1 year of age at the time of consent/assent
- Confirmed diagnosis of PA based on diagnosis by molecular genetic testing (biallelic *PCCA* and/or *PCCB* variants)
- Patient and/or legally authorized representative is willing and able to provide informed consent and/or assent as mandated by local regulations and willing and able to comply with study-related assessments
- Sexually active females of childbearing potential and sexually active males of reproductive potential agree to use a highly effective method of contraception during study treatment and for 3 months following the last administration of study drug

Key Exclusion Criteria

- Laboratory abnormalities achieving exclusionary thresholds
- eGFR <30 mL/min/1.73 m^2, or chronic dialysis
- QTc >480 msec using Bazett's correction
- Positive pregnancy test/pregnant or breastfeeding
- Grade 3 or 4 heart failure
- History or planned organ transplant
- Hypersensitivity or contraindication to premedications
- History of hypersensitivity to components of the drug
- Another investigational agent within 30 days or within 5 elimination half-lives
- Major surgical procedure within 30 days (excludes line, port, or feeding tube)
- Enrollment not deemed to be of clinical benefit, in the opinion of the PI
- Other condition that could interfere with interpretation of study results or limit the participation in the study, in the opinion of the PI
- COVID-19 vaccination within 6 weeks between last dose and first study drug administration

eGFR, estimated glomerular filtration rate; PA, propionic acidemia; PI, principal investigator; QTc, corrected QT interval.

Patient Disposition (as of March 31, 2023)

- **16 patients dosed with mRNA-3927**

2 patients discontinued mRNA-3927-P101 (1 withdrawal by patient; 1 following AEs)

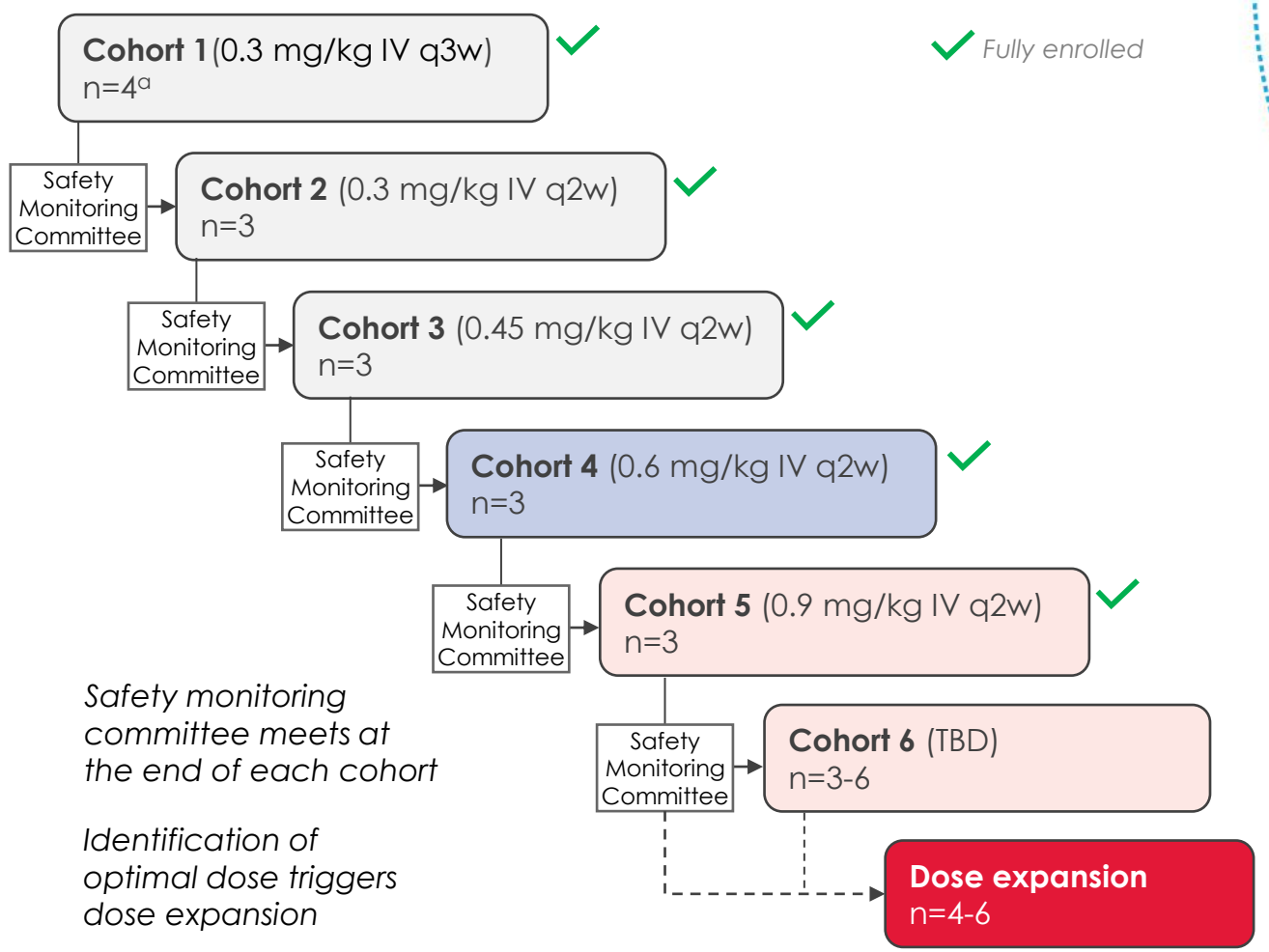
- **All 11 patients completing mRNA-3927-P101 have continued in the extension study**
- **In mRNA-3927-P101 and the extension:**

>280 intravenous doses of mRNA-3927 administered

>13 patient-years' experience with mRNA-3927

5 patients with >1 year of dosing

- **Results are presented for mRNA-3927-P101 and the extension study**



[a]An additional patient was enrolled in Cohort 1 per-protocol following discontinuation of 1 patient after their first dose.
q3w, every 3 weeks; q2w, every 2 weeks; IV, intravenous; TBD, to be determined.

Patient Demographics and Baseline Characteristics

	Cohort 1 0.3 mg/kg q3w (n=4)	Cohort 2 0.3 mg/kg q2w (n=3)	Cohort 3 0.45 mg/kg q2w (n=3)	Cohort 4 0.6 mg/kg q2w (n=3)	Cohort 5 0.9 mg/kg q2w (n=3)	All (n=16)
Age at enrollment, years Median (range)	15.4 (5.2-26.8)	2.3 (1.5-8.3)	3.8 (1.6-15.3)	8.8 (1.3-21.4)	15.1 (1.4-17.8)	**8.5 (1.3-26.8)**
Age at disease onset, months Median (range)	0.0 (0-1)	0.0 (0-0)	0.0 (0-1)	1.5 (0-3)[a]	0.0 (0-0)[a]	**0.0 (0-3)**
Sex, n						
Male:female	2:2	0:3	2:1	2:1	2:1	**8:8**
Race, n						
Asian	3	0	1	0	1	**5**
Black or African American	0	0	1	0	1	**2**
White	1	2	1	2	1	**7**
Other	0	1	0	1	0	**2**
Ethnicity, n						
Not Hispanic or Latino	4	3	3	3	3	**16**
Weight						
Weight at baseline, kg Median (range)	44.4 (21.6-66.5)	15.8 (10.6-24.8)	18.0 (11.2-42.7)	24.9 (11.9-62.7)	39.3 (11.7-88.1)	**24.7 (10.6-88.1)**
Genotype						
PCCA:PCCB	2:2	1:2	2:1	2:1	1:2	**8:8**

[a]Data missing for 1 patient.

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Most Common Treatment-Emergent Adverse Events [n (%)]

	Cohort 1 0.3 mg/kg q3w	Cohort 2 0.3 mg/kg q2w	Cohort 3 0.45 mg/kg q2w	Cohort 4 0.6 mg/kg q2w	Cohort 5 0.9 mg/kg q2w	All
Patients initially assigned, n	4	3	3	3	3	**16**
Patients receiving at least 1 dose,[a] n	4	5	3	3	3	**16**
Total number of doses, n	71	118	56	27	16	**288**
Treatment exposure, person-years	4.3	4.8	2.2	1.2	0.6	**13.6**
TEAEs[b] occurring in >2 patients overall, n (%)						
Pyrexia	3 (75.0)	3 (60.0)	1 (33.3)	2 (66.7)	1 (33.3)	**10 (62.5)**
Diarrhea	2 (50.0)	4 (80.0)	1 (33.3)	1 (33.3)	0	**7 (43.8)**
Vomiting	1 (25.0)	4 (80.0)	1 (33.3)	2 (66.7)	0	**7 (43.8)**
Cough	1 (25.0)	3 (60.0)	1 (33.3)	1 (33.3)	0	**5 (31.3)**
COVID-19	1 (25.0)	3 (60.0)	0	1 (33.3)	0	**5 (31.3)**
Upper respiratory tract infection	1 (25.0)	2 (40.0)	1 (33.3)	1 (33.3)	0	**5 (31.3)**
Diaper dermatitis	1(25.0)	2 (40.0)	0	1 (33.3)	0	**4 (25.0)**
Rhinorrhea	0	3 (60.0)	1 (33.3)	0	0	**4 (25.0)**
Ear pain	1 (25.0)	2 (40.0)	1 (33.3)	0	0	**3 (18.8)**
Gastroenteritis	1 (25.0)	0	0	2 (66.7)	0	**3 (18.8)**
Increased creatinine phosphokinase	2 (50.0)	0	1 (33.3)	0	0	**3 (18.8)**
Increased lipase	0	1 (20.0)	0	0	2 (66.7)	**3 (18.8)**
Metabolic disorder	2 (50.0)	1 (20.0)	0	0	0	**3 (18.8)**

Includes both mRNA-3927-P101and extension studies.
[a]Patients may change dosing regimens and will be counted and summarized in each regimen if they received at least 1 dose in the regimen. [b]TEAEs are defined as AEs reported on or after the date that the intervention began.
q2w, every 2 weeks; q3w, every 3 weeks; TEAE, treatment-emergent adverse event.

Safety Summary

- **No dose-limiting toxicities occurred**
- **TEAEs[a] were reported in 15/16 patients and drug-related TEAEs were reported in 9/16 patients**
- **SAEs[b] were reported in 8/16 patients**

  There were 2/16 patients who reported a total of 3 drug-related SAEs:
  - Grade 3 pancreatitis in 1 patient
  - Vascular device infection and injection-site reaction (both grade 2) consistent with infusion site reactions in 1 patient

  Overall, of 54 reported SAEs, 31 were considered related to PA
- **Infusion-related reactions[c] (IRRs) occurred in 6/16 patients and in 19/288 doses (6.6%)**

  1 patient had IRR in 11 out of 39 doses received

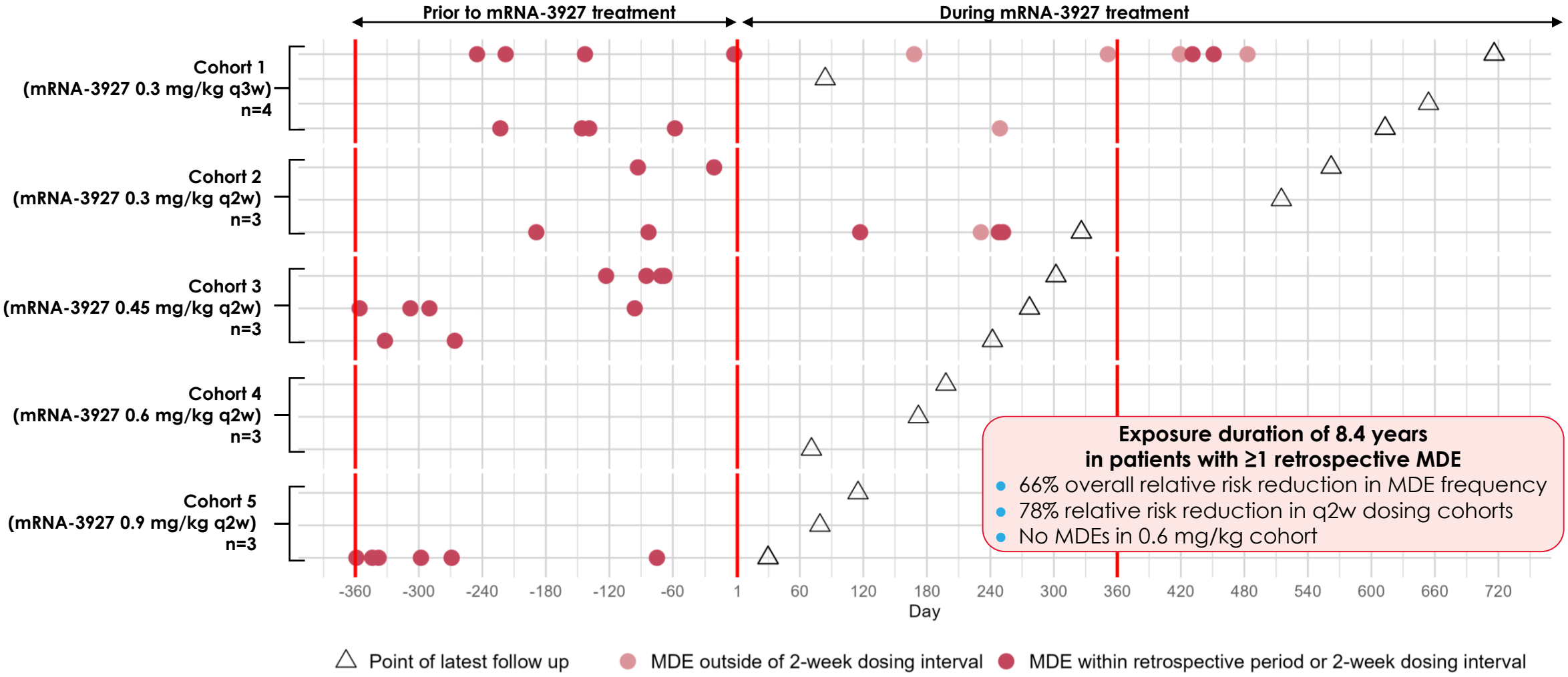
  3/6 patients had IRRs in 2 doses and 2/6 patients had IRRs in 1 dose

  All IRRs were grade 1 or 2
- **Three hypersensitivity reactions occurred in 1 patient**

Grade 1-2 rash with dose 1; grade 1 rash with dose 2; no reactions thereafter

Includes both mRNA-3927-P101 and extension studies.
[a]TEAEs are defined as AEs reported on or after the date that the intervention began. [b]An AE is considered an SAE if, in the view of the Investigator or Sponsor, it results in any of the following outcomes: death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, persistent disability/incapacity, a congenital anomaly/birth defect, or is judged as medically important. [c]Infusion-related reactions (IRRs) are defined as a drug-related AE occurring withing 24 hours of the start of a dose.
AE, adverse event; IRR, infusion-related reaction; PA, propionic acidemia; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Summary of Metabolic Decompensations Events (MDEs)



Includes mRNA-3927-P101 and extension studies.
The generalized linear mixed models for MDE number and duration includes period, dosing frequency, and period-by-dosing frequency as independent variables, duration of observation as an offset and a random effect to consider the repeated measurements within a patient.
q2w, every 2 weeks; q3w, every 3 weeks; MDE, metabolic decompensation event.

Conclusions

- **This is the first clinical trial reporting results of an mRNA therapeutic for intracellular protein replacement**
- **16 patients dosed**

>280 intravenous doses of mRNA-3927

5 patients received >1 year of dosing

More than 13 patient-years' experience on drug

All eligible participants continue to opt-in to the open-label expansion

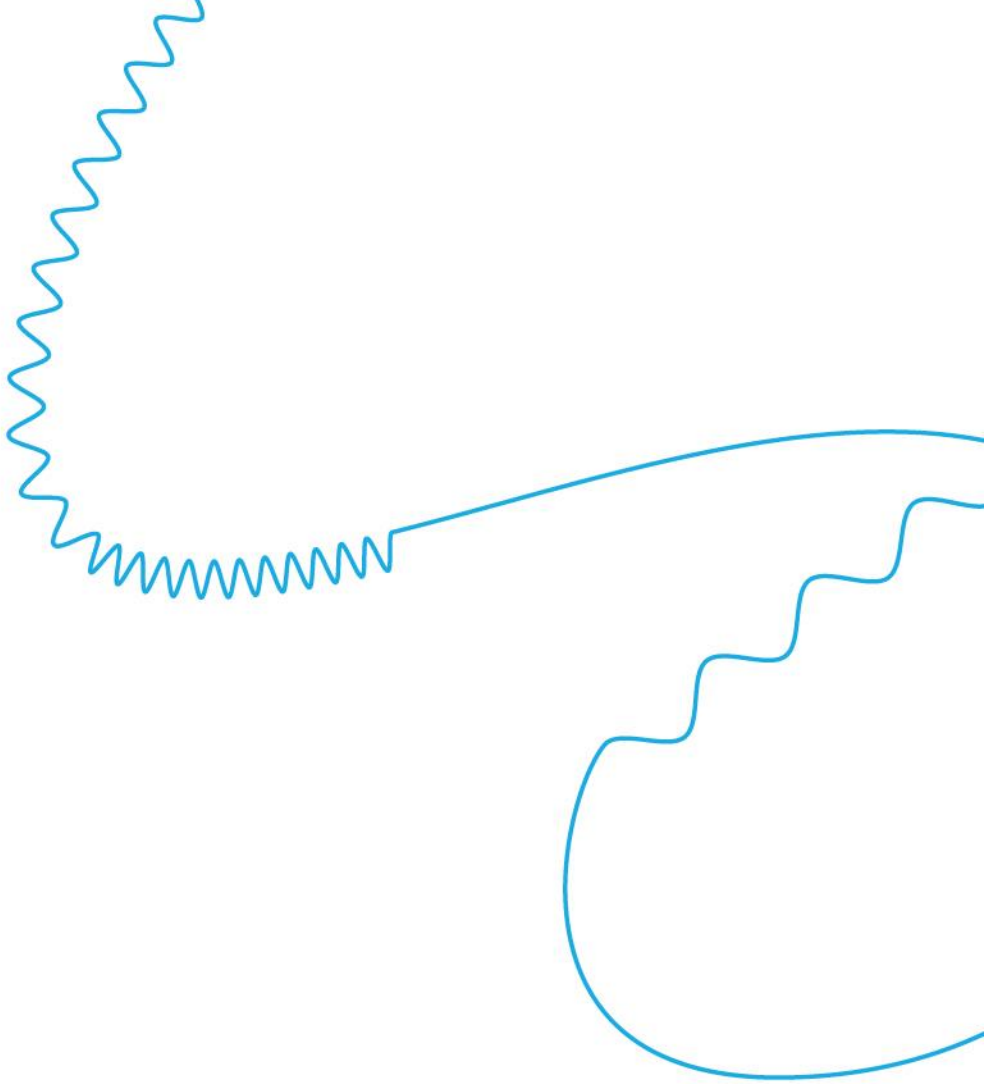
- **To date, mRNA-3927 has been well-tolerated in patients with PA at the doses administered, with no dose-limiting toxicities**
- **Results show encouraging early signs of potential clinical benefit with mRNA-3927**

Reductions in the number of metabolic decompensation events were observed after the start of mRNA-3927 treatment in patients who reported them in the 12 months prior to dosing

- **The study is ongoing**

Next steps include confirming the optimal therapeutic dose and evaluating it in additional patients, including infants

Thank you



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Forward-looking statements

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 on a path to registration. 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.