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

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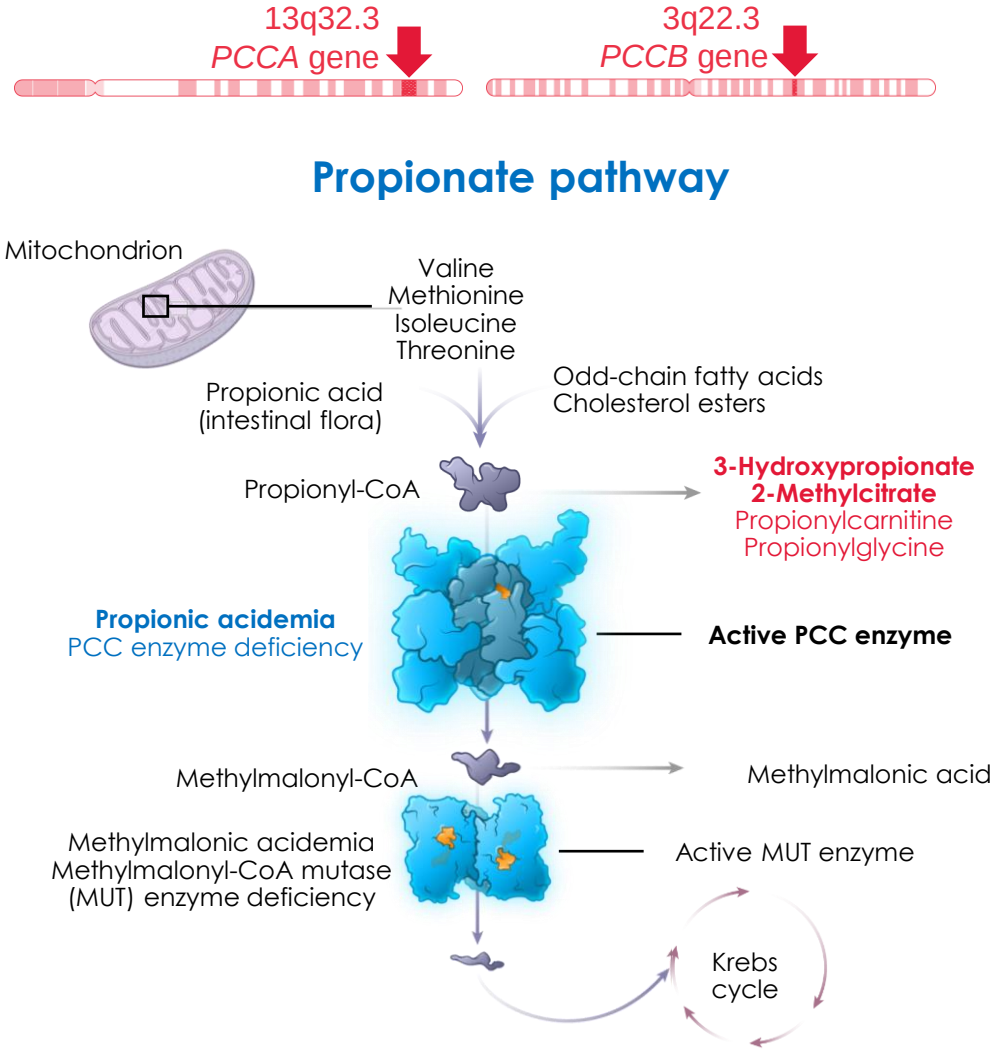
Propionic Acidemia (PA) Is a Rare Inherited Metabolic Disorder

- **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]



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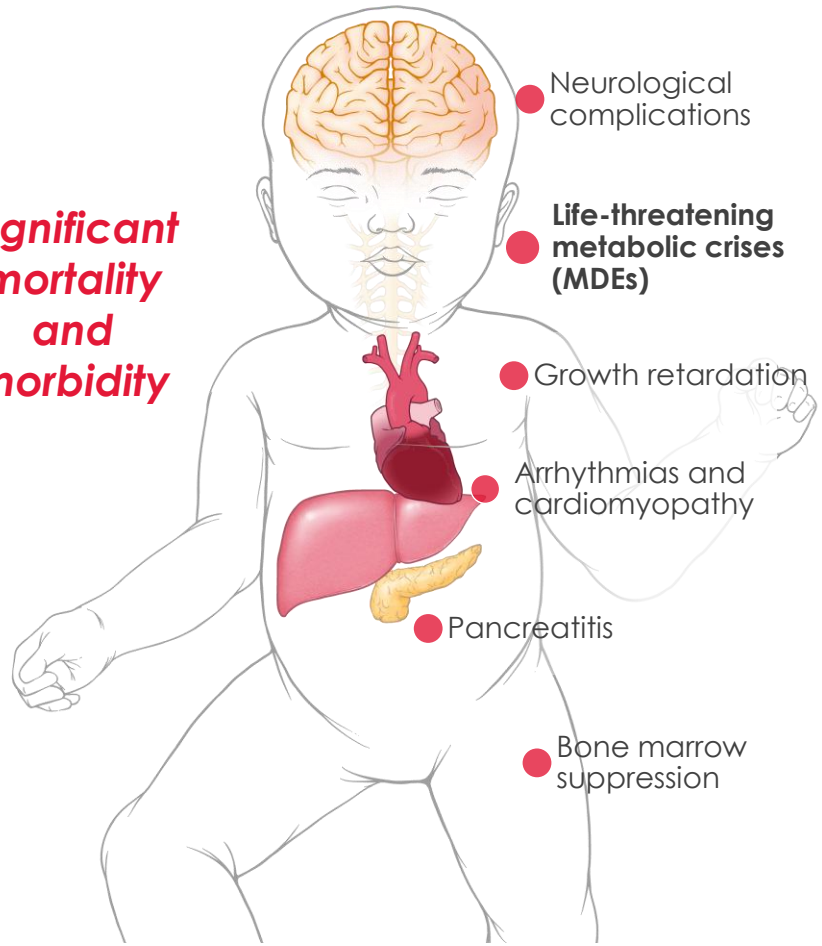
Clinical Characteristics and Management of PA

- 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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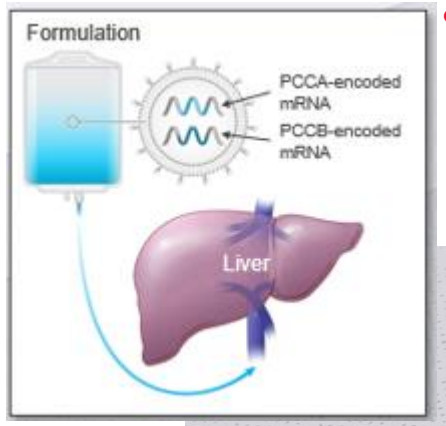
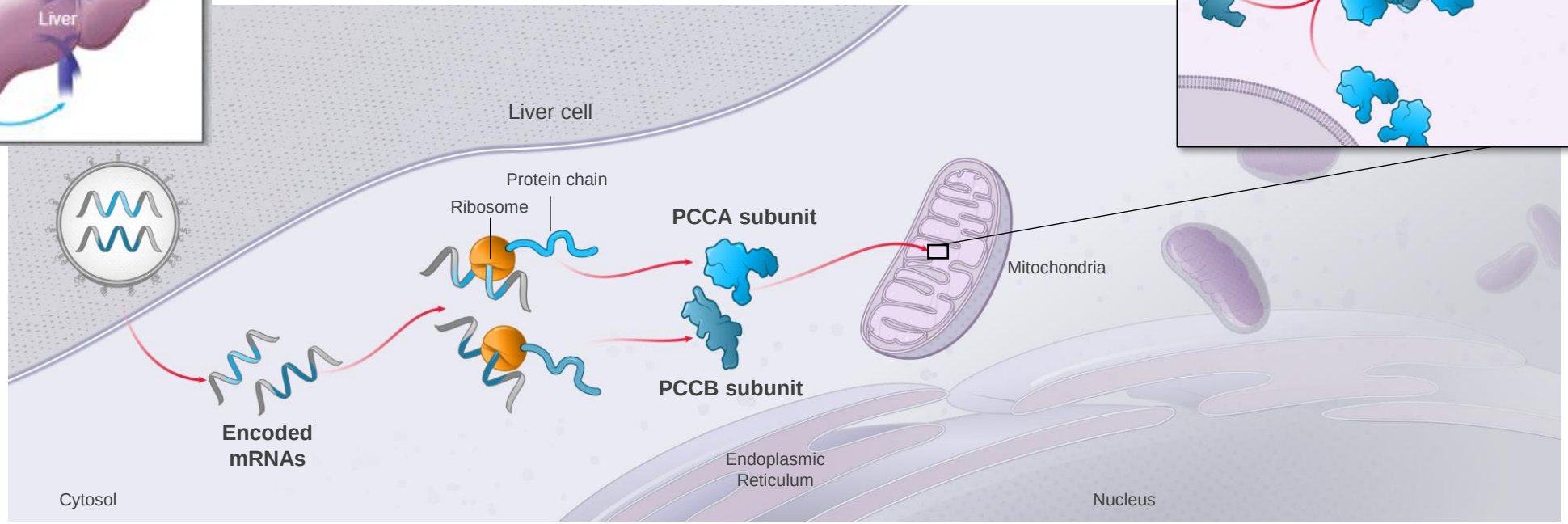
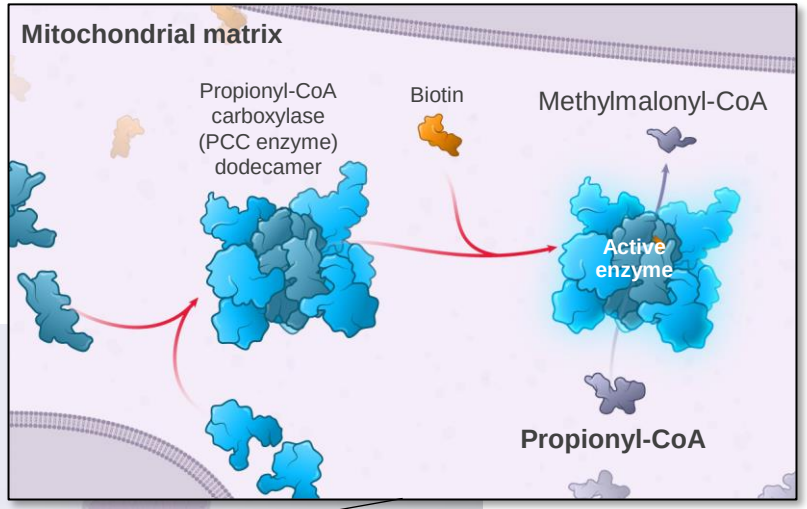
An Introduction to mRNA-3927

- **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**



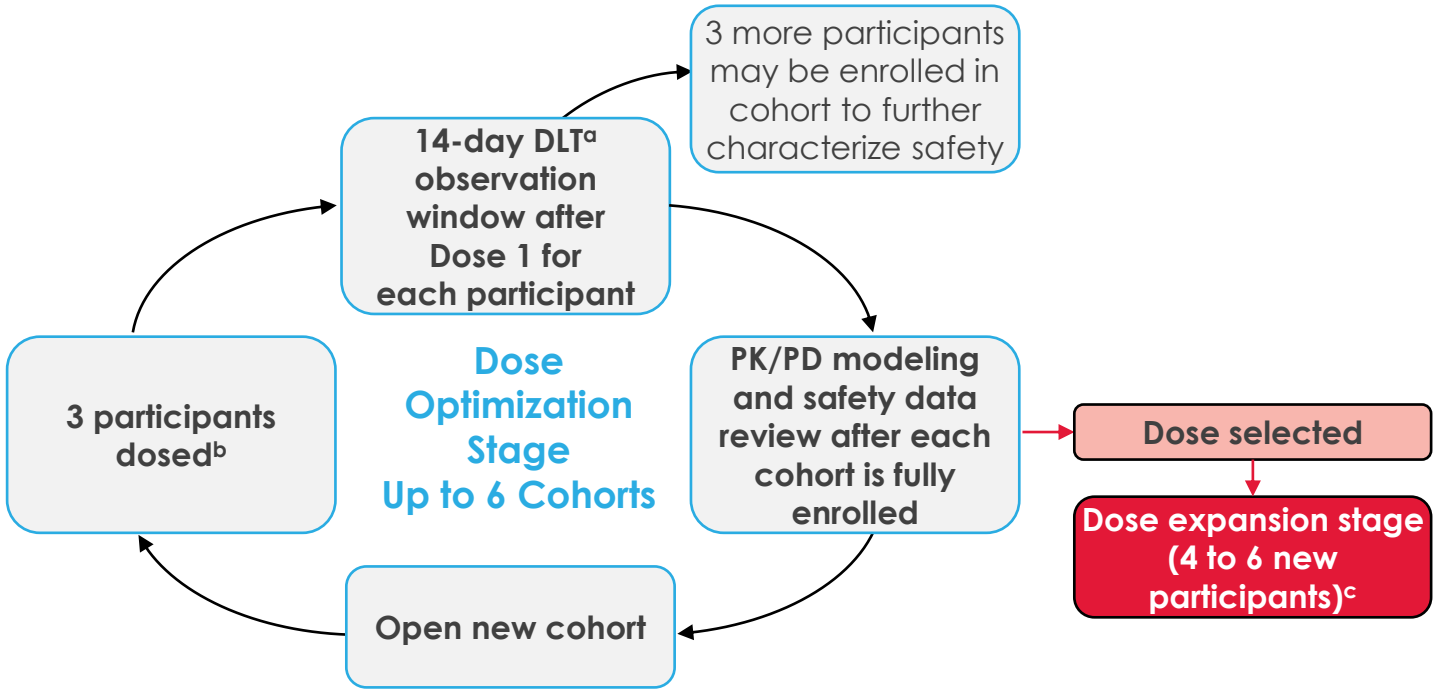




IV, intravenous.

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

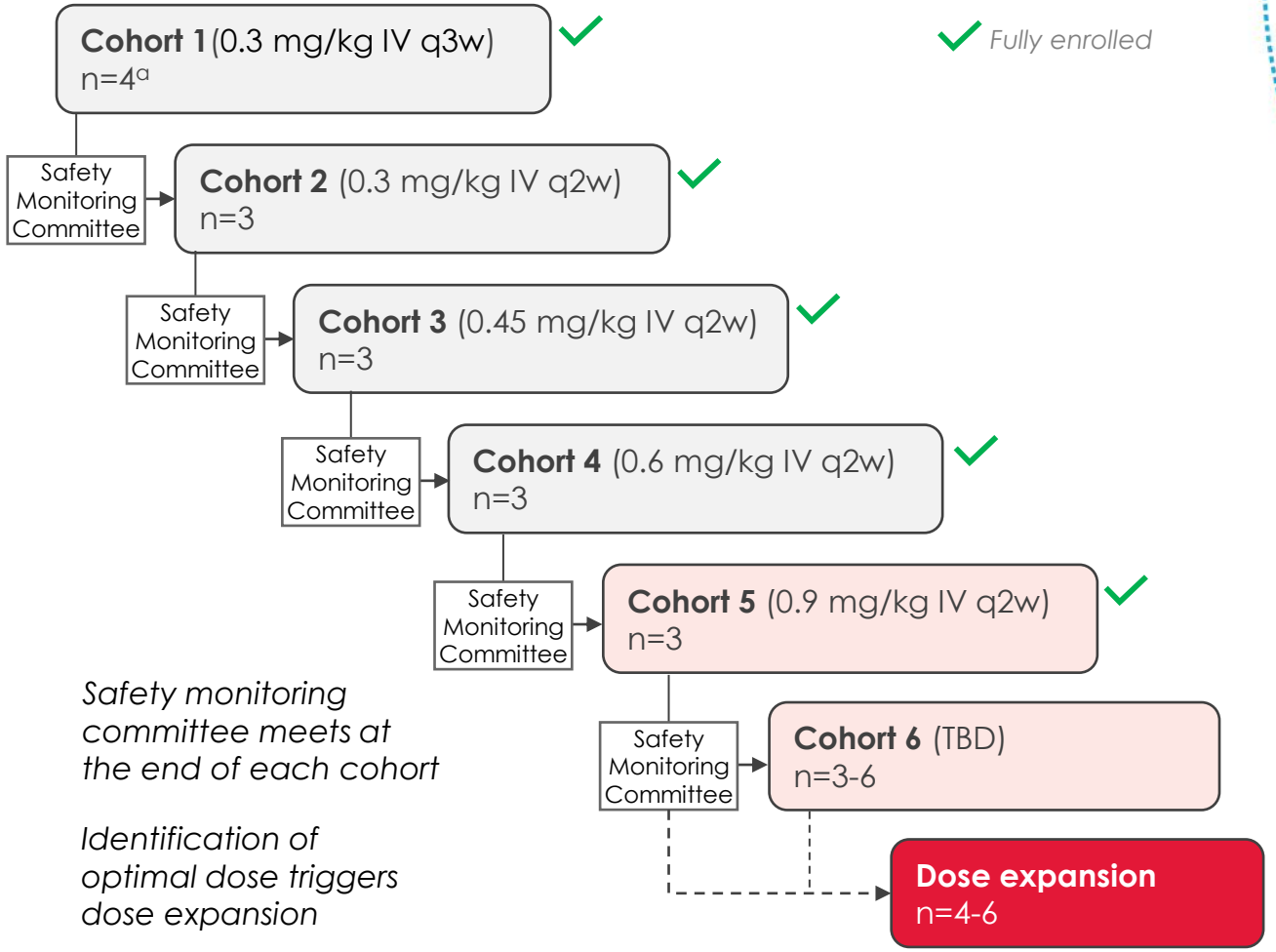
Key Exclusion Criteria

- 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.

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)**

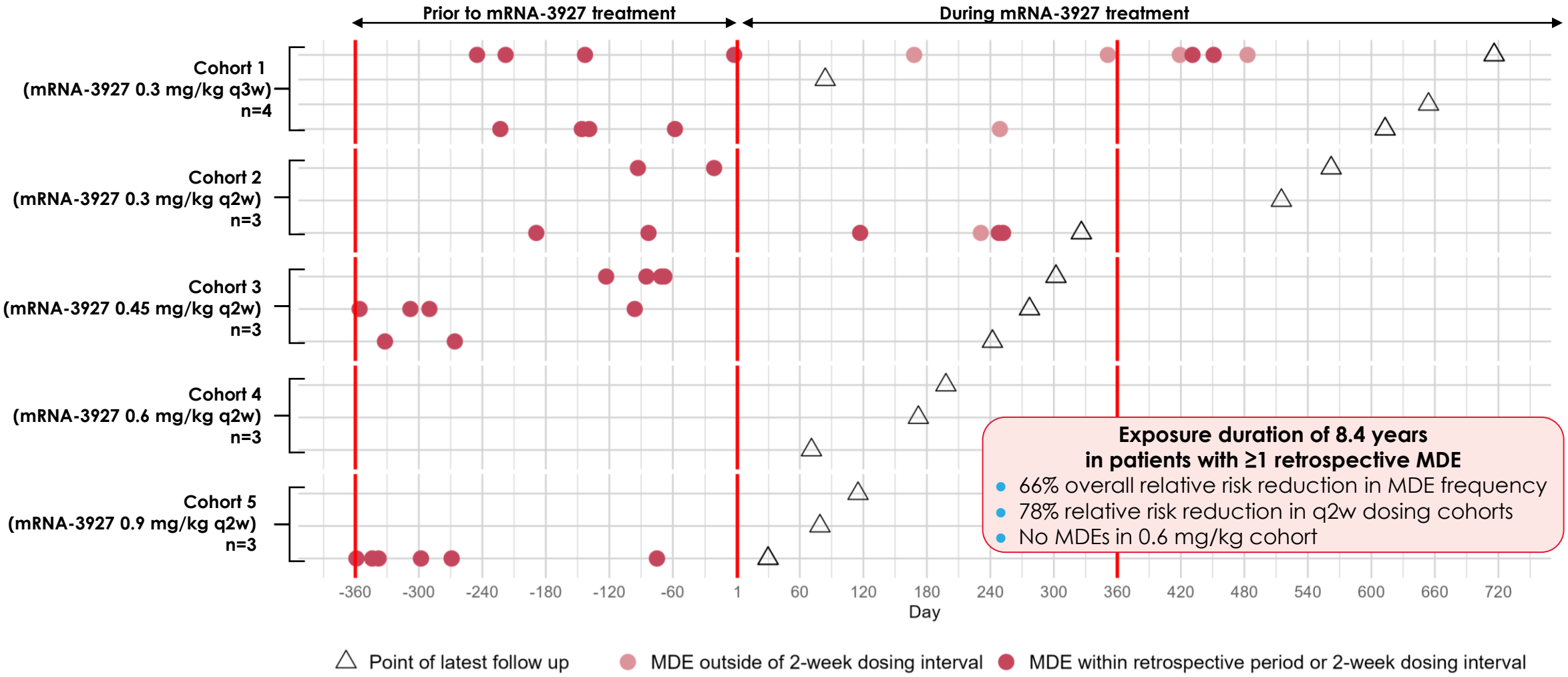
Includes both mRNA-3927-P101and extension studies.
[a]Patients may change dosing regimens and will be counted and summarized in each regimen if they received at least 1 dose in the regimen. [b]TEAEs are defined as AEs reported on or after the date that the intervention began.
q2w, every 2 weeks; q3w,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

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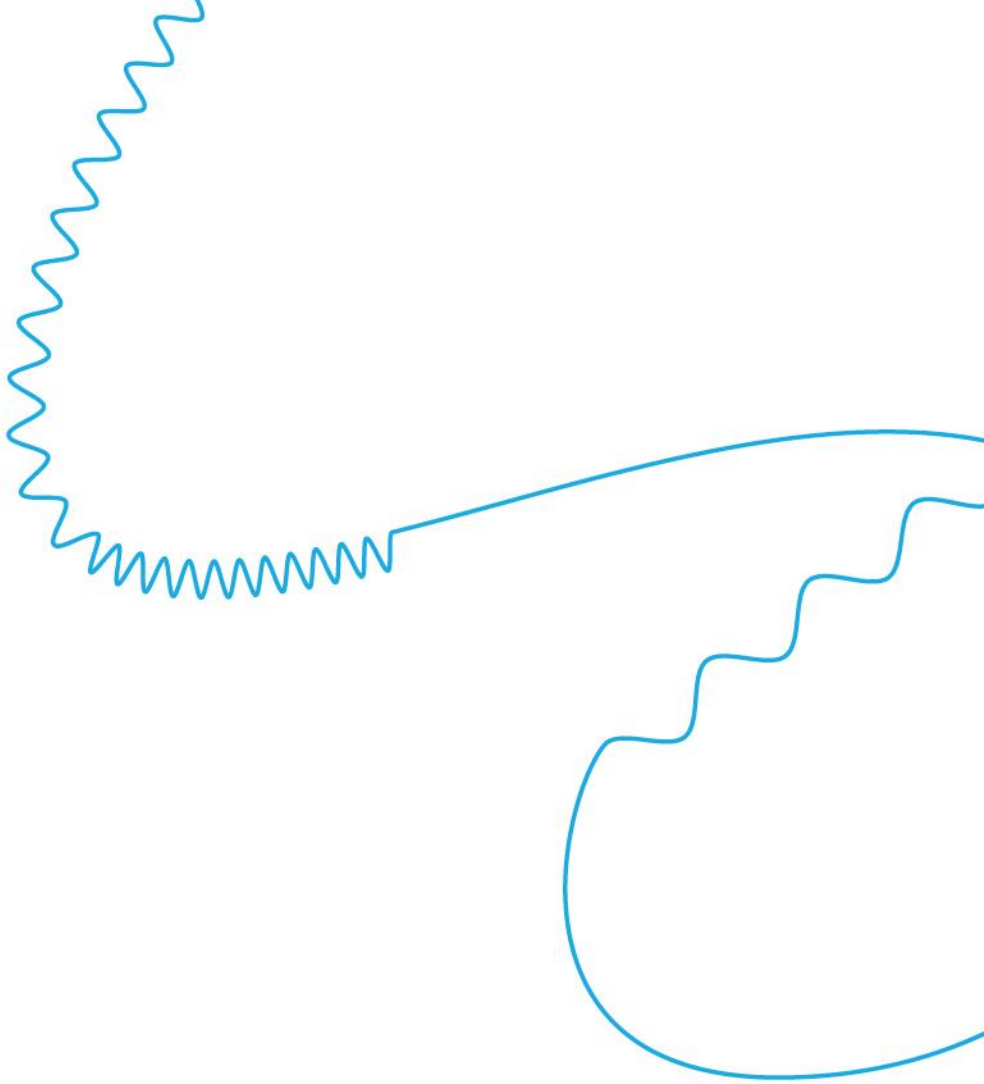
Thank you



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