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

- **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

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

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, arrhythmias, 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)

- 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)

- 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

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\(^a\)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 m², 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

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Cohort 1 (0.3 mg/kg IV q3w)
- n=4
- Fully enrolled

Cohort 2 (0.3 mg/kg IV q2w)
- n=3

Cohort 3 (0.45 mg/kg IV q2w)
- n=3

Cohort 4 (0.6 mg/kg IV q2w)
- n=3

Cohort 5 (0.9 mg/kg IV q2w)
- n=3

Cohort 6 (TBD)
- n=3-6

Identification of optimal dose triggers
dose expansion

Safety monitoring committee meets at the end of each cohort

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### Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>0.3 mg/kg q3w (n=4)</th>
<th>0.3 mg/kg q2w (n=3)</th>
<th>0.45 mg/kg q2w (n=3)</th>
<th>0.6 mg/kg q2w (n=3)</th>
<th>0.9 mg/kg q2w (n=3)</th>
<th>All (n=16)</th>
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</thead>
<tbody>
<tr>
<td>Age at enrollment, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>15.4 (5.2-26.8)</td>
<td>2.3 (1.5-8.3)</td>
<td>3.8 (1.6-15.3)</td>
<td>8.8 (1.3-21.4)</td>
<td>15.1 (1.4-17.8)</td>
<td>8.5 (1.3-26.8)</td>
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<tr>
<td>Age at disease onset, months</td>
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<tr>
<td>Median (range)</td>
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<td>0.0 (0-1)</td>
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<td>0.0 (0-3)</td>
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<td>Sex, n</td>
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<td>Male:female</td>
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<td>2:1</td>
<td>8:8</td>
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<td>3</td>
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<td>3</td>
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<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Weight at baseline, kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range)</td>
<td>44.4 (21.6-66.5)</td>
<td>15.8 (10.6-24.8)</td>
<td>18.0 (11.2-42.7)</td>
<td>24.9 (11.9-62.7)</td>
<td>39.3 (11.7-88.1)</td>
<td>24.7 (10.6-88.1)</td>
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<tr>
<td>Genotype</td>
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<td></td>
<td></td>
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<td>PCCA:PCCB</td>
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<td>1:2</td>
<td>2:1</td>
<td>2:1</td>
<td>1:2</td>
<td>8:8</td>
</tr>
</tbody>
</table>

Note: Data missing for 1 patient.
## Most Common Treatment-Emergent Adverse Events [n (%)]

<table>
<thead>
<tr>
<th></th>
<th>Cohort 1 0.3 mg/kg q3w</th>
<th>Cohort 2 0.3 mg/kg q2w</th>
<th>Cohort 3 0.45 mg/kg q2w</th>
<th>Cohort 4 0.6 mg/kg q2w</th>
<th>Cohort 5 0.9 mg/kg q2w</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients initially assigned, n</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Patients receiving at least 1 dose, n</td>
<td>4</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Total number of doses, n</td>
<td>71</td>
<td>118</td>
<td>56</td>
<td>27</td>
<td>16</td>
<td>288</td>
</tr>
<tr>
<td>Treatment exposure, person-years</td>
<td>4.3</td>
<td>4.8</td>
<td>2.2</td>
<td>1.2</td>
<td>0.6</td>
<td>13.6</td>
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</table>

**TEAEs**

<table>
<thead>
<tr>
<th>Event</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>3 (75.0)</td>
<td>3 (60.0)</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>1 (33.3)</td>
<td>10 (62.5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (50.0)</td>
<td>4 (80.0)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (25.0)</td>
<td>4 (80.0)</td>
<td>1 (33.3)</td>
<td>2 (66.7)</td>
<td>0</td>
<td>7 (43.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>1 (25.0)</td>
<td>3 (60.0)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>COVID-19</td>
<td>1 (25.0)</td>
<td>3 (60.0)</td>
<td>0</td>
<td>1 (33.3)</td>
<td>0</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>1 (25.0)</td>
<td>2 (40.0)</td>
<td>1 (33.3)</td>
<td>1 (33.3)</td>
<td>0</td>
<td>5 (31.3)</td>
</tr>
<tr>
<td>Diaper dermatitis</td>
<td>1 (25.0)</td>
<td>2 (40.0)</td>
<td>0</td>
<td>1 (33.3)</td>
<td>0</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>0</td>
<td>3 (60.0)</td>
<td>1 (33.3)</td>
<td>0</td>
<td>0</td>
<td>4 (25.0)</td>
</tr>
<tr>
<td>Ear pain</td>
<td>1 (25.0)</td>
<td>2 (40.0)</td>
<td>1 (33.3)</td>
<td>0</td>
<td>0</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1 (25.0)</td>
<td>0</td>
<td>0</td>
<td>2 (66.7)</td>
<td>0</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Increased creatinine phosphokinase</td>
<td>2 (50.0)</td>
<td>0</td>
<td>1 (33.3)</td>
<td>0</td>
<td>0</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Increased lipase</td>
<td>0</td>
<td>1 (20.0)</td>
<td>0</td>
<td>0</td>
<td>2 (66.7)</td>
<td>3 (18.8)</td>
</tr>
<tr>
<td>Metabolic disorder</td>
<td>2 (50.0)</td>
<td>1 (20.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3 (18.8)</td>
</tr>
</tbody>
</table>

Includes both mRNA-3927-101 and extension studies.

*Patients may change dosing regimens and will be counted and summarized in each regimen if they received at least 1 dose in the regimen. **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

\(^a\)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 within 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)

Prior to mRNA-3927 treatment

Exposure duration of 8.4 years in patients with ≥1 retrospective MDE

- 66% overall relative risk reduction in MDE frequency
- 78% relative risk reduction in q2w dosing cohorts
- No MDEs in 0.6 mg/kg cohort

Cohort 1 (mRNA-3927 0.3 mg/kg q3w) n=4
Cohort 2 (mRNA-3927 0.3 mg/kg q2w) n=3
Cohort 3 (mRNA-3927 0.45 mg/kg q2w) n=3
Cohort 4 (mRNA-3927 0.6 mg/kg q2w) n=3
Cohort 5 (mRNA-3927 0.9 mg/kg q2w) n=3

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.

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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