## Propionic acidemia (PA) (mRNA-3927)

**Last program update: May 6, 2021**

<table>
<thead>
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<th>Modality</th>
<th>ID  #</th>
<th>Program Indication</th>
<th>Preclinical development</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3 and commercial</th>
<th>Moderna rights</th>
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<td><strong>Systemic intracellular therapeutics</strong></td>
<td>mRNA-3927</td>
<td>PCCA/PCCB, Propionic acidemia, PA</td>
<td>Preclinical development</td>
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<td>mRNA-3705</td>
<td>MUT, Methylmalonic acidemia, MMA</td>
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Propionic acidemia (PA) overview

• **Disease overview:** Rare, autosomal recessive organic acidemia/aciduria, caused by PCC mitochondrial enzyme deficiency
  – The PCC enzyme is a dodecamer made up of alpha (PCCA) and beta (PCCB) subunits
  – PCC deficiency arises out of a mutation in PCCA (PA Type I) or PCCB (PA Type II)

• **Clinical manifestations:** Characterized by recurrent episodes of life-threatening metabolic decompensations as well as progressive multi-organ damage (neurological, cardiac, pancreatic, renal, etc.)

• **Prevalence:** ~1:100-250K births
  – ~325-2,000 patients in the US

• Primarily a **pediatric disease** with majority of cases presenting within 3 days of life
  – Significant mortality & morbidity

• **Treatment:** There is no approved therapy for PA
  – Standard of care included dietary and palliative measures
  – Liver transplant shown to improve biochemical and clinical outcomes
Propionic acidemia (mRNA-3927) Phase 1/2 Paramount Study

Key objective
• To evaluate the safety and pharmacology of mRNA-3927 in patients 1 year of age and older with propionic acidemia (PA)

Primary endpoint
• Safety
• Pharmacokinetics
• Pharmacodynamics

Secondary endpoint
• Incidence and severity of adverse events (AEs)
• Change in plasma biomarkers: methlycitric acid (2-MC) and Hydroxypropionic acid (3-HP)

Trial progress
• Phase 1/2 enrolling patients
• First patient enrolled

Dose Optimization Stage (up to 5 cohorts)

Open new cohort

3 participants dosed¹

PK/PD modeling and safety data review after each cohort is fully enrolled

21-day DLT observation window after dose 1 for each participant

3 more participants may be enrolled in cohort to further characterize safety

Dose Expansion Stage (4 to 6 new participants)²

Dose Selected

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 subtype (PCCA and PCCB) will be enrolled
A diagnosis of propionic acidemia isn't all that's shaping life these days.
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