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

*Last program update: October 29, 2020*

<table>
<thead>
<tr>
<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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<tbody>
<tr>
<td></td>
<td>mRNA-3927</td>
<td>PCCA/PCCB Propionic acidemia, PA</td>
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<td>Worldwide</td>
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<td></td>
<td>mRNA-3705</td>
<td>MUT Methylmalonic acidemia, MMA</td>
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<td>Worldwide</td>
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<td>mRNA-3283</td>
<td>PAH Phenylketonuria, PKU</td>
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<td>mRNA-3745</td>
<td>G6Pase Glycogen storage disease type 1a, GSD1a</td>
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**Systemic intracellular therapeutics**
Organic acidemias

Multiple candidates targeting same metabolic pathway

MMA and PA

- Similar biology and disease pathology
- Shared treating clinicians and centers of excellence
- Relative prevalence in any given locale is a function of local founder effects/consanguinity
  - MMA: ~500-2,000 patients in the US*
  - PA: ~325-2,000 patients in the US*

*M based on estimated birth prevalence (MMA: 0.3-1.2:100,000 newborns; PA: 0.2-1.2:100,000 newborns) and mortality rates

mRNA advantages

- Ability to encode for intracellular proteins, localized to mitochondria
- Ability to titrate dose to response
- Potential to treat during acute metabolic decompensations
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 PCB (PA Type II)

• **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

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<th>Clinical manifestations</th>
<th>Neonatal period</th>
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<tr>
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<td>Neurological complications</td>
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<tr>
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<td>Optic atrophy</td>
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<td>Growth retardation</td>
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<td>Arrhythmias &amp; cardiomyopathy</td>
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<td>Life-threatening metabolic crises</td>
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<td>Pancreatitis</td>
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Propionic acidemia program update

Propionic Acidemia (PA)
(mRNA-3927)

- Chronic treatment for patients with propionic acidemia which replaces the missing or dysfunctional mitochondrial enzyme propionyl-CoA carboxylase (PCC)

- mRNA-3927 has received FDA Fast Track Designation, FDA orphan drug designation, FDA rare pediatric disease designation and EMA orphan drug designations
  - Open IND

- Protocol amendment during COVID-19 pause:
  - Amended our protocol to a novel dose-optimization clinical trial design
  - Less burdensome on patients, their families and our clinical partners
  - Plan to launch an extension study for continued dosing of patients upon positive risk/benefit profile from Phase 1/2 trial
Propionic acidemia (mRNA-3927) Phase 1/2 trial protocol amended to a novel dose optimization trial

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: methylicitic acid (2-MC) and Hydroxypropionic acid (3-HP)

Trial progress
• Site initiation was paused due to COVID-19 disruptions
• Study start-up has resumed

Dose Optimization Stage
(up to 5 cohorts)

- 3 participants dosed
- 21-day DLT observation window after dose 1 for each participant
- PK/PD modeling and safety data review after each cohort is fully enrolled
- 3 more participants may be enrolled in cohort to further characterize safety

Dose Expansion Stage
(4 to 6 new participants)

- 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
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