Propionic acidemia (PA) (mRNA-3927)

Last program update: September 17, 2020

<table>
<thead>
<tr>
<th>Modality</th>
<th>ID #</th>
<th>Program Description</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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</thead>
<tbody>
<tr>
<td>Systemic intracellular therapeutics</td>
<td>mRNA-3704</td>
<td>MUT Methylmalonic acidemia, MMA</td>
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<td>Worldwide</td>
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<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-3283</td>
<td>PAH Phenylketonuria, PKU</td>
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<td></td>
<td>mRNA-3745</td>
<td>G6Pase Glycogen storage disease type 1a, GSD1a</td>
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<td>Worldwide</td>
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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*

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

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

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

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**Dose Optimization Stage** (up to 5 cohorts)

1. **Patient enrolled**
2. **Open new cohort**
3. **3 participants dosed**
4. **21-day DLT observation window after dose 1 for each participant**
5. **PK/PD modeling and safety data review after each cohort is fully enrolled**

**Dose Expansion Stage** (4 to 6 new participants)

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

**Dose Selected**

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**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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