Methylmalonic acidemia (MMA) (mRNA-3705)

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>Systemic intracellular therapeutics</td>
<td>mRNA-3927</td>
<td>PCCA/PCCB, Propionic acidemia, PA</td>
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<td></td>
<td>mRNA-3705</td>
<td>MUT, Methylmalonic acidemia, MMA</td>
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<td>mRNA-3283</td>
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<td>mRNA-3745</td>
<td>G6Pase, Glycogen storage disease type 1a, GSD1a</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
Methylmalonic acidemia (MMA) overview

- **Disease overview:** Rare, autosomal recessive organic acidemia/aciduria
  - Defective or deficient MUT enzyme (methylmalonic CoA mutase)

- Disease is progressive, involves multiple organ systems and is highly lethal; includes risk of life-threatening metabolic decompensation episodes

- Primarily a pediatric disease with onset in early infancy; significant mortality and morbidity

- **Prevalence:** ~1:100K (except in the Middle East where it is higher, 6:100K)

- **Treatment:** There is no approved therapy for MMA
  - Current interventions include: dietary restriction, cofactor therapy and carnitine
  - Liver and/or kidney transplant is the only effective treatment, even in infants (but transplant is not curative)

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### Clinical manifestations

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<th>Neonatal period</th>
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<td>Neurological complications</td>
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<td>Growth retardation</td>
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<td>High mortality</td>
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<td>Life-threatening metabolic crises</td>
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<td>Pancreatitis</td>
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<td>Renal complications</td>
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MMA program update

Methylmalonic Acidemia (MMA) (mRNA-3705)

• Chronic treatment for patients with methylmalonic acidemia which replaces faulty enzyme methylmalonic-CoA mutase (MUT)

• Due to COVID-19, enrollment and new site initiation was paused for methylmalonic acidemia (MMA; mRNA-3704)

• R&D Day 2020 (September 17, 2020): We have leveraged the pause due to COVID-19 to improve clinical trial design and bring forward a next generation product (mRNA-3705)
Moving forward with next generation MMA candidate (mRNA-3705)

MMA (mRNA-3705)

- Introduction of a drug product with better pharmacology (new mRNA)
- Same LNP, also used in mRNA-1944
- Taken opportunity to revise clinical protocol to improve patient experience and operational feasibility
- Received rare pediatric disease designation for next generation MMA candidate (mRNA-3705)

Next steps

- File new IND and CTA applications for mRNA-3705

mRNA-3705 produces higher levels of hMUT enzyme in the liver of rats

mRNA-3705 showed greater potency and prolonged lowering of MMA in mut- mice

*P<0.05, ***P<0.001, ****P<0.0001 by one-way ANOVA followed by Tukey’s multiple comparisons test
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