moderna

Rare disease therapeutics

Program Pack

# Methylmalonic acidemia (MMA) (mRNA-3705)

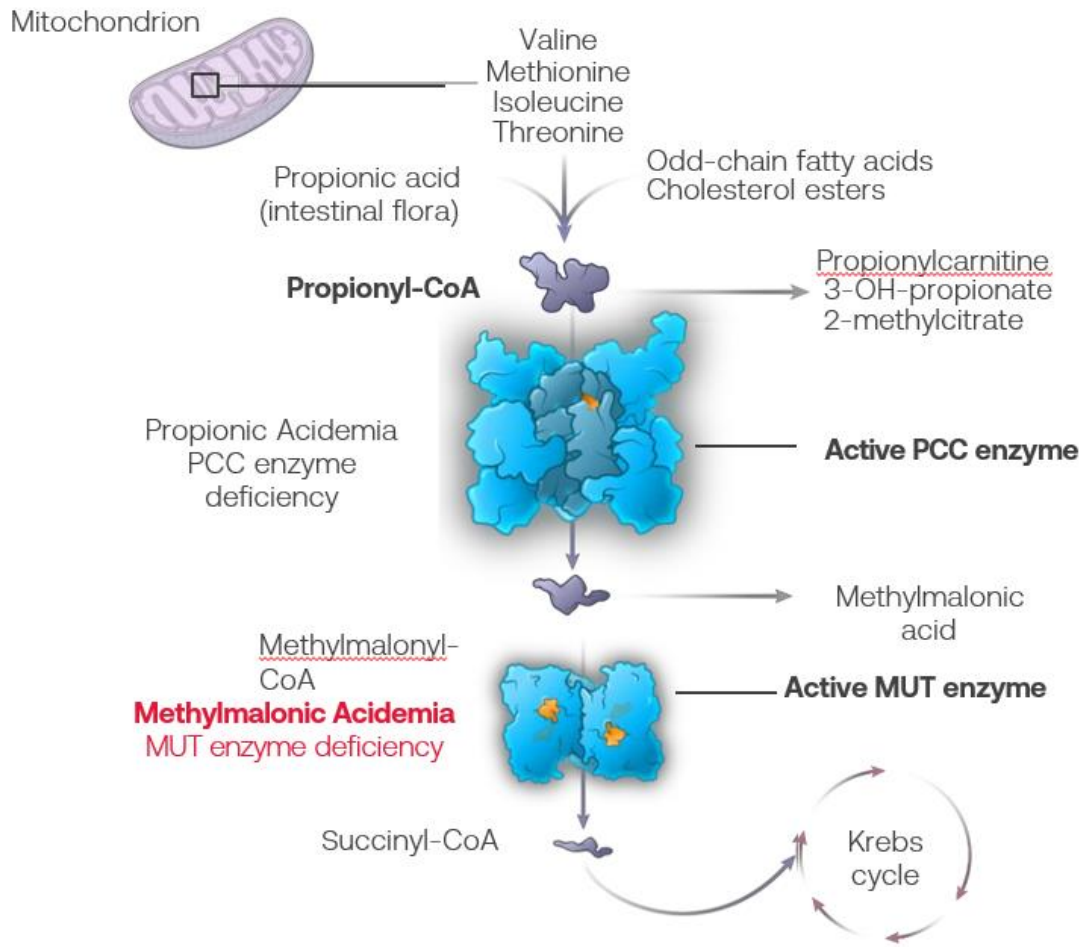
# Overview of Methylmalonic Acidemia (MMA) due to MUT deficiency

Methylmalonic acidemia (MMA) refers to a rare, autosomal recessive acidemia

It is caused by a defective or missing MUT enzyme (methylmalonic CoA mutase)

**Changes in the *MMUT gene* cause methylmalonic acidemia**

- Gene provides instructions for making an enzyme called methylmalonyl CoA mutase
- Changes in the gene disrupt the function of the enzyme and prevent the normal breakdown of molecules



# Methylmalonic acidemia (MMA) has no approved therapies

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

**Treatment:** There is no approved therapy for MMA

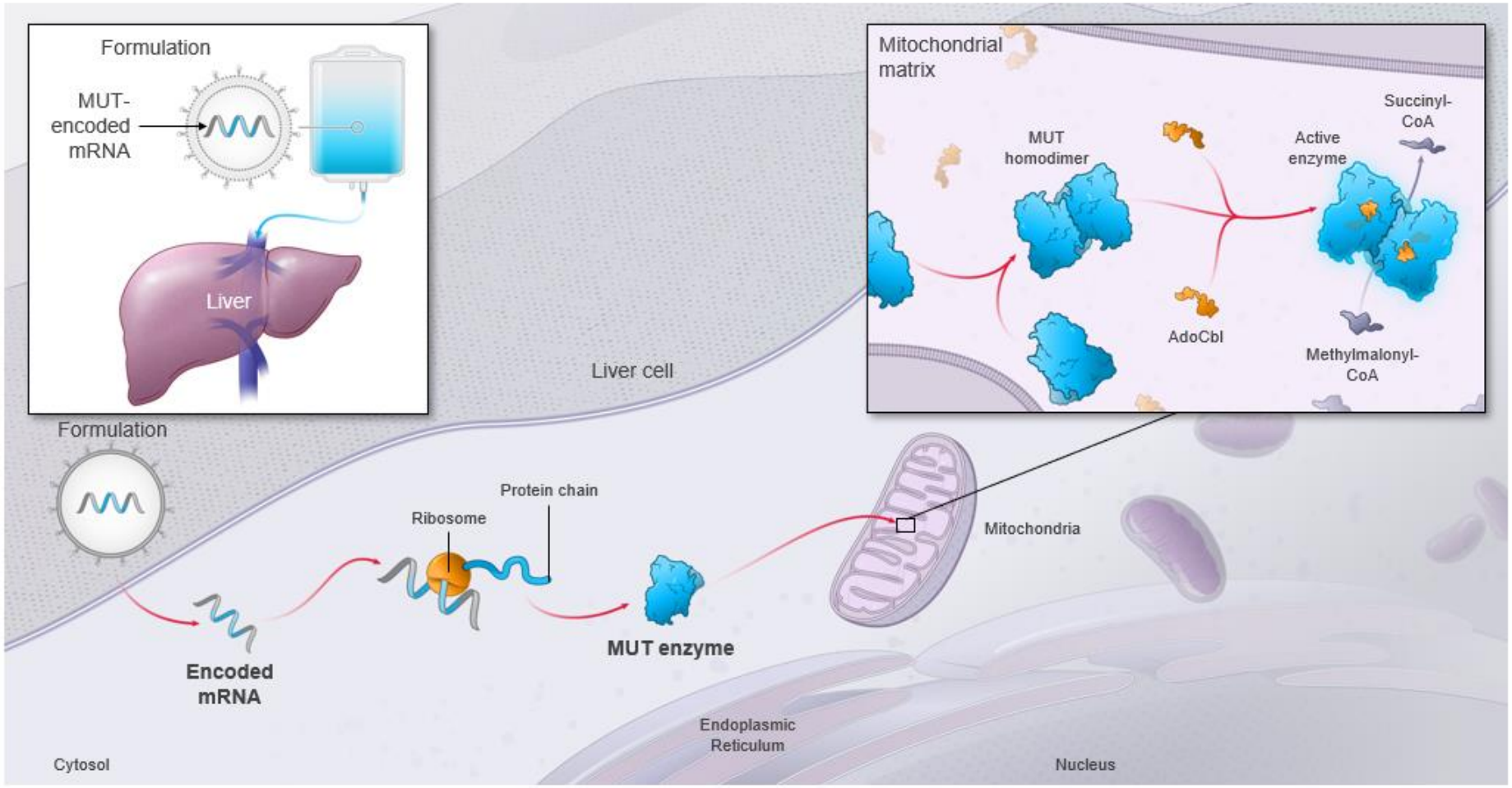
**Current interventions include:**

- Protein-restricted diet, carnitine supplementation
- Carbaglu® approved for the treatment of hyperammonemia
- Liver and/or kidney transplant

## MMA Clinical Manifestations

- Recurrent episodes of **life-threatening metabolic decompensations**
- **Progressive multi-organ damage**
  - Brain damage
  - Seizures
  - Intellectual disability
  - Severe vision problems
  - Inflammation of the pancreas (pancreatitis)
  - Chronic renal failure
  - Heart failure (cardiomyopathy); heart rhythm problems
  - Increased risk of having a metabolic stroke as early as a few weeks of age
  - Osteoporosis which can lead to fractures
  - Hematologic: reduced number of cells in blood (anemia, leukopenia, thrombocytopenia, pancytopenia)
  - Growth retardation

# mRNA-3705 encodes the intracellular MUT enzyme




Note: AdoCbl = cofactor adenosylcobalamin

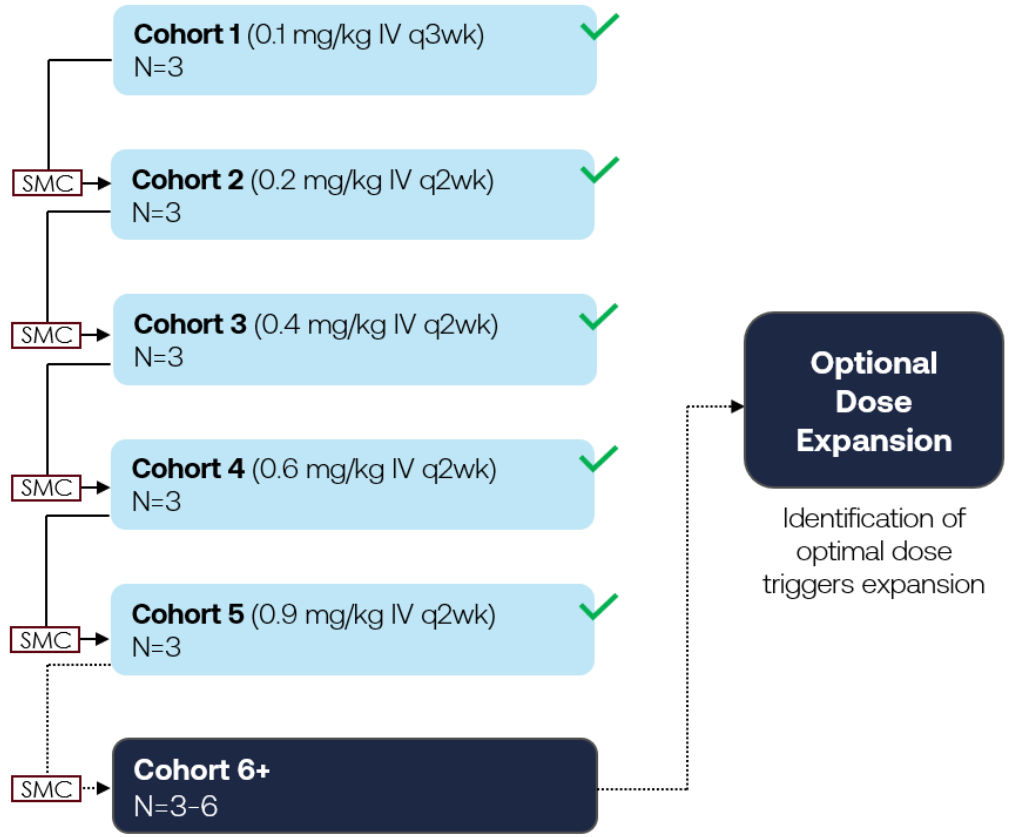
# Ongoing Phase 1/2 Study designed to evaluate safety and pharmacology of mRNA-3705 in participants with MMA

## Dose Optimization Stage Endpoints

- **Primary endpoints:** safety and tolerability
- **Secondary endpoints:** Pharmacokinetic parameters and change in blood methylmalonic acid and 2-methylcitrate (2-MC)
- **Exploratory clinical endpoints:** Include metabolic decompensation events (MDEs), MMA-related hospitalizations, patient-centered outcome measures

**Treatment period is 10 doses, after which participants may enter an extension study**

**P101 Dose Optimization Design (3 + 3 design)**



# mRNA-3705-P101: summary of demographics and baseline characteristics

| | Cohort 1<br>0.1 mg/kg Q3W<br>(N=3) | Cohort 2<br>0.2 mg/kg Q2W<br>(N=3) | Cohort 3<br>0.4 mg/kg Q2W<br>(N=3) | Cohort 4<br>0.6 mg/kg Q2W<br>(N=3) | Cohort 5<br>0.9 mg/kg Q2W<br>(N=3) | Total<br>(N=15) |
|---|---|---|---|---|---|---|
| Age at enrollment, median (years) | 12.17 | 2.67 | 7.83 | 18.75 | 6.08 | 7.83 |
| Min, Max | 4.5, 14.4 | 2.5, 39.5 | 5.8, 16.0 | 4.3, 32.6 | 3.1, 8.5 | 2.5, 39.5 |
| Age at disease onset, median (months) | 0 | 0 | 3 | 11 | 0 | 0 |
| Min, Max | 0 | 0, 1 | 0, 10 | 0, 117 | 0, 52 | 0, 117 |
| **Sex, n** | | | | | | |
| Male | 1 | 1 | 1 | 2 | 3 | 8 |
| Female | 2 | 2 | 2 | 1 | 0 | 7 |
| **Weight** | | | | | | |
| Weight at baseline, median (kg) | 25.2 | 13.2 | 22.6 | 60.1 | 22.5 | 22.6 |
| Min, Max | 19.5, 40.7 | 12.2, 57.1 | 16.2, 53.4 | 16.3, 66.0 | 17.0, 23.2 | 12.2, 66.0 |
| **Phenotype** | | | | | | |
| Mut0 | 3 | 3 | 3 | 2 | 2 | 13 |
| Mut- | 0 | 0 | 0 | 1 | 1 | 2 |



moderna

# mRNA-3705-P101: clinical experience to date

**As of April 8, 2024***

- **Fifteen participants have been dosed**, with a total of 384 doses administered
- **Total cumulative treatment duration among all participants is ~17.3 patient-years**
  - Median treatment duration among all participants is 1.05 patient-years
  - Maximum participant treatment duration is 2.3 patient-years
- **Generally well-tolerated to date** with no discontinuations due to safety and no events meeting protocol-defined dose-limiting toxicity criteria
- **All participants who have completed the treatment period of the main study have opted to enter a long-term extension study**
- **Both P101 and Extension studies are ongoing**

*Data include both on-going mRNA-3705-P101 and Extension studies

# Safety in mRNA-3705-P101: overall summary as-of April 2024

**No deaths or discontinuations due to safety-related reasons**

Three discontinuations in the extension for non-safety reasons

**No events meeting dose-limiting toxicity criteria have been observed**

**1 serious adverse event (AE) assessed as related to mRNA-3705 by the investigator:**
Event of "body temperature increased" (CTCAE grade 2, resolved). Patient has continued on treatment

**Drug related adverse events were mostly mild or moderate (CTCAE grade 1 or 2)**

**Most common AEs are pyrexia (n=5), upper respiratory tract infection (n=5), and vomiting (n=5)**

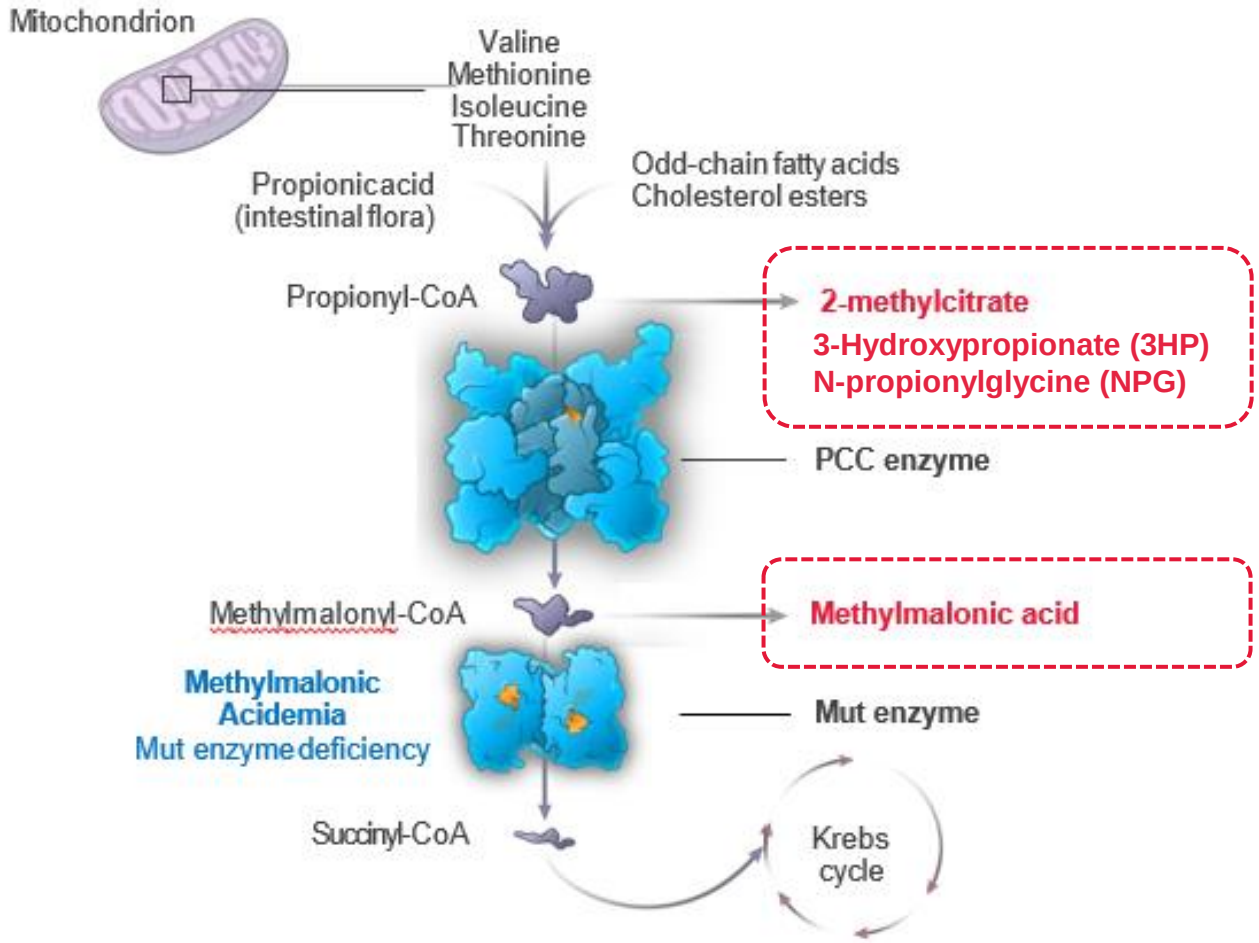
**Less than 5% of administered doses associated with infusion-related reactions**

# Biomarkers to evaluate pharmacodynamics of mRNA-3705

Methylmalonic acid and 2-methylcitrate represent **primary biomarkers** proximal to the enzyme deficiency

Changes in concentrations of methylmalonic acid generally **correlate with disease severity** and natural history data suggest that changes in methylmalonic acid may be associated with clinical events

There are **no clinically validated** biomarkers for MMA



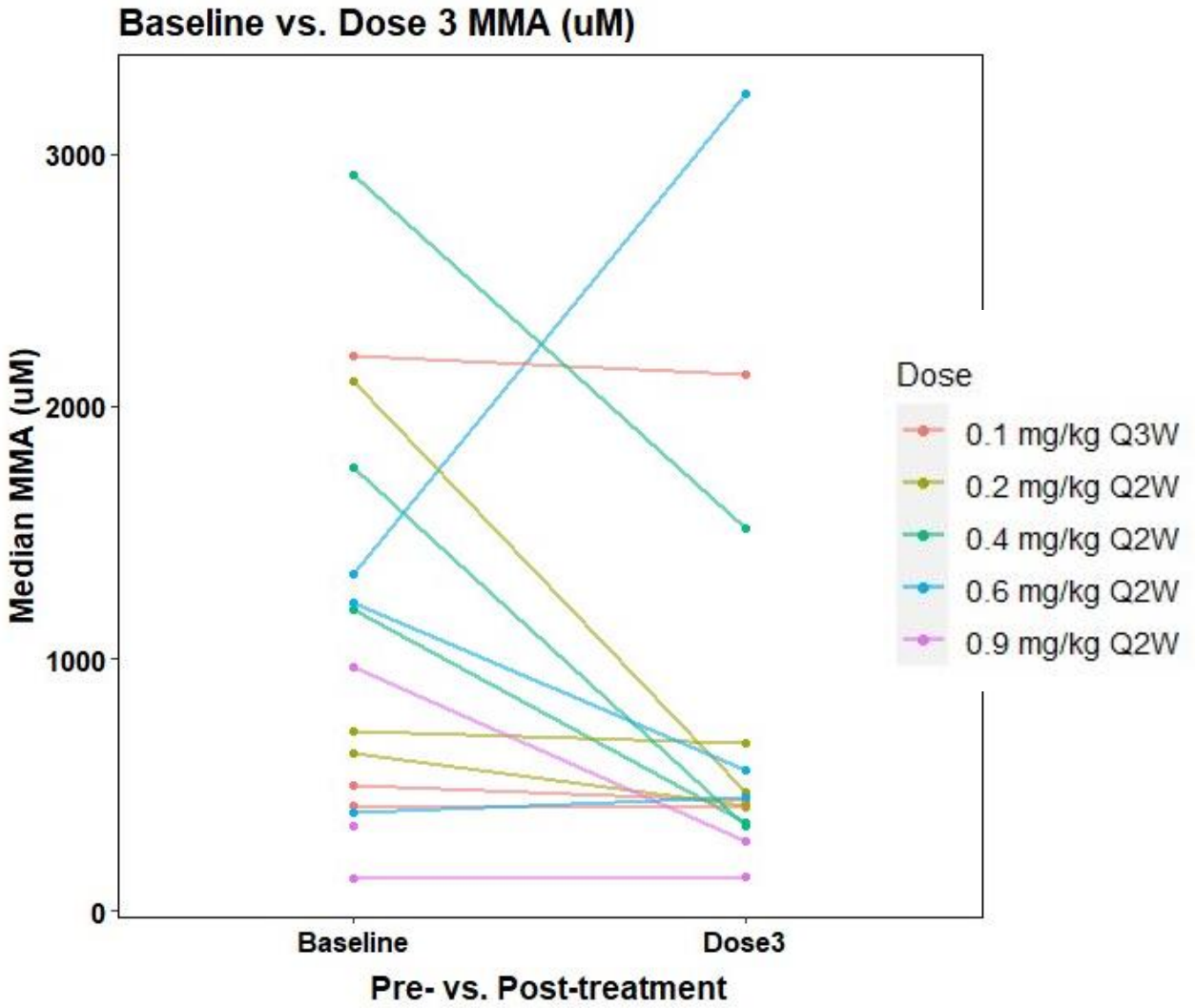

*Data include both on-going mRNA-3705-P101 and Extension studies

# mRNA-3705-P101: pattern of biomarker response mirrors that seen in liver transplant

Methylmalonic acid and 2-methylcitrate represent **primary biomarkers** proximal to the enzyme deficiency

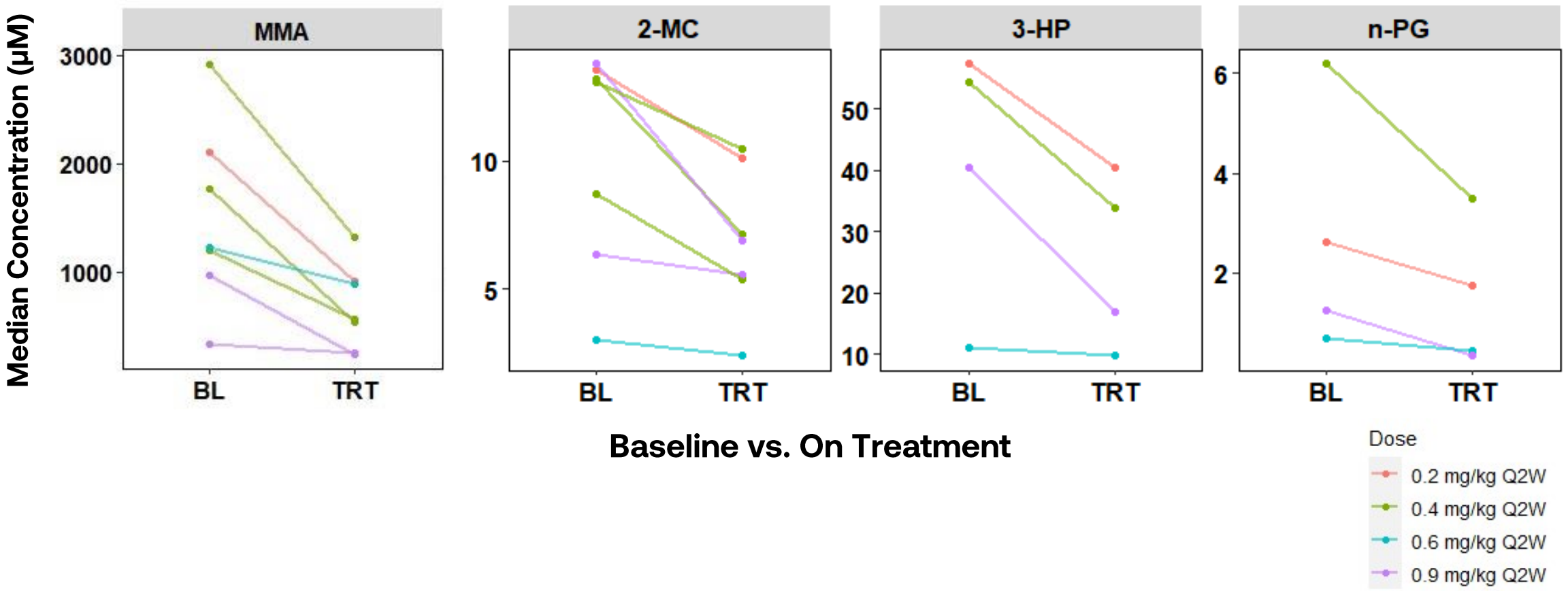
Changes in concentrations of methylmalonic acid generally **correlate with disease severity** and natural history data suggest that changes in methylmalonic acid may be associated with clinical events

There are **no clinically validated** biomarkers for MMA



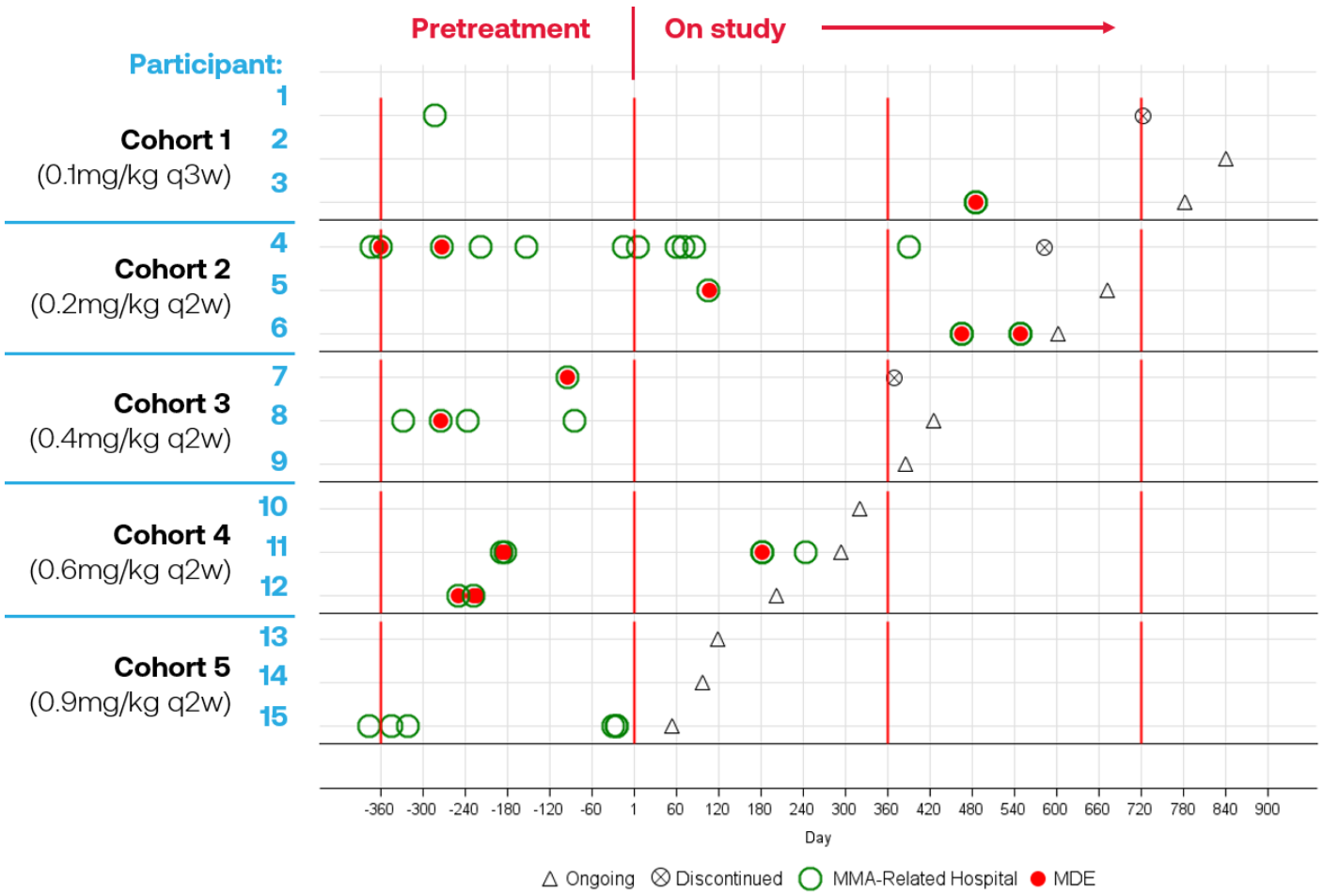

*Data include both on-going mRNA-3705-P101 and Extension studies

# mRNA-3705-P101: Participants who demonstrate reductions in MMA also show changes in other pathway biomarkers



# mRNA-3705-P101: Promising initial data on clinical endpoints

**Trends towards fewer MMA-related hospitalizations and Metabolic Decompensation Events (MDEs) (as-of April, 2024)**




## MMA-related hospitalizations

**Year prior to study entry:**
0.95/year
(SE: 0.4)
**On study:**
0.5/year
(SE: 0.248)

## MDEs

**Year prior to study entry:**
0.57/year
(SE: 0.249)
**On study:**
0.28/year
(SE: 0.133)

SE: Standard Error

# US FDA Support for Clinical Trials Advancing Rare Disease Therapeutics (START) Pilot Program

As part of FDA's initiative to **accelerate the pace of development** in rare diseases, mRNA-3705 was **1 of 4 programs** to be accepted into the CBER START pilot program on May 29, 2024.

## Features

- Enhanced regulatory interactions beyond formal meetings to allow for rapid, more frequent ad-hoc communication mechanisms
- Access to all review disciplines
- Milestone driven to support significant regulatory activities (initiation of pivotal study, pre-BLA meeting)

***CAMBRIDGE, MA / ACCESSWIRE / June 6, 2024 /*** *Moderna, Inc. (NASDAQ:MRNA) today announced that the U.S. Food and Drug Administration (FDA) has selected mRNA-3705 for the Support for Clinical Trials Advancing Rare Disease Therapeutics (START) pilot program. mRNA-3705 is an investigational therapeutic for methylmalonic acidemia (MMA) due to methylmalonic-CoA mutase (MUT) deficiency.*

**"We are excited about this opportunity and proud that our investigational mRNA therapeutic for MMA was selected by the U.S. FDA for the START pilot program. This selection highlights the promise of Moderna's innovative mRNA platform beyond vaccines and the potential this novel medicine may have in addressing the serious and unmet medical needs of MMA," said Kyle Holen, M.D., Moderna's Senior Vice President and Head of Development, Therapeutics and Oncology. "Selection for this program will enable enhanced communication with the U.S. FDA, resulting in acceleration of our development program as we prepare for pivotal study initiation for mRNA-3705 in 2024."**

# Summary and next steps

**Clinical Results and Experience**

- Early results suggest potential decreases in annualized rates of MMA-related hospitalizations and MDEs compared to pre-treatment ratees
- Reductions in methylmalonic acid and other pathway biomarkers in participants, particularly at doses of at least 0.4 mg/kg Q2W
- Cumulative treatment duration of over 17 patient years

**Safety**

- Generally well-tolerated to date with no discontinuations due to safety and no events meeting protocol-defined dose-limiting toxicity criteria

**Next steps**

- Continued engagement with FDA (via START) and other global regulators
- Expects to start registrational study in 2025

# Medical and scientific presentations

## 2024 SIMD (MDE Score)

https://s29.q4cdn.com/435878511/files/doc_presentations/2024/Apr/14/sikirica_simd-2024-1-59.pdf

## ASGCT 2022 (rare disease strategy)

https://s29.q4cdn.com/435878511/files/doc_presentations/2022/05/ASGCT-2022-(May-17)-Strategies-for-Developing-mRNA-Based-Therapeutics-for-Rare-Diseases.pdf

# Forward-looking statement

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding clinical studies; potential market size; and Moderna's expectation for mRNA-3705 to start registrational study in 2025. In some cases, forward-looking statements can be identified by terminology such as “may,” “should,” “expects,” “intends,” “plans,” “aims,” “anticipates,” “believes,” “estimates,” “predicts,” “potential,” “continue,” or the negative of these terms or other comparable terminology, although not all forward -looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties and other factors, many of which are beyond Moderna’s control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties and other factors include those described in Moderna’s most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna’s current expectations and speak only as of the date referenced on the first page.