Methylmalonic acidemia (MMA) (mRNA-3705)

Last updated 5/2/24

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial
Rare disease intracellular therapeutics	**Propionic acidemia (PA)**	mRNA-3927					
	Methylmalonic acidemia (MMA)	mRNA-3705					
	Glycogen storage disease type 1a (GSD1a)	mRNA-3745					
	Ornithine transcarbamylase deficiency (OTC)	mRNA-3139					
	Phenylketonuria (PKU)	mRNA-3210					
Inhaled pulmonary therapeutics	**Crigler-Najjar syndrome type 1 (CN-1)**	mRNA-3351					
	Cystic fibrosis (CF)*	mRNA-3692 / VX-522					
Cardiovascular therapeutics	**Relaxin**	mRNA-0184					

*Vertex to pay milestone and royalties

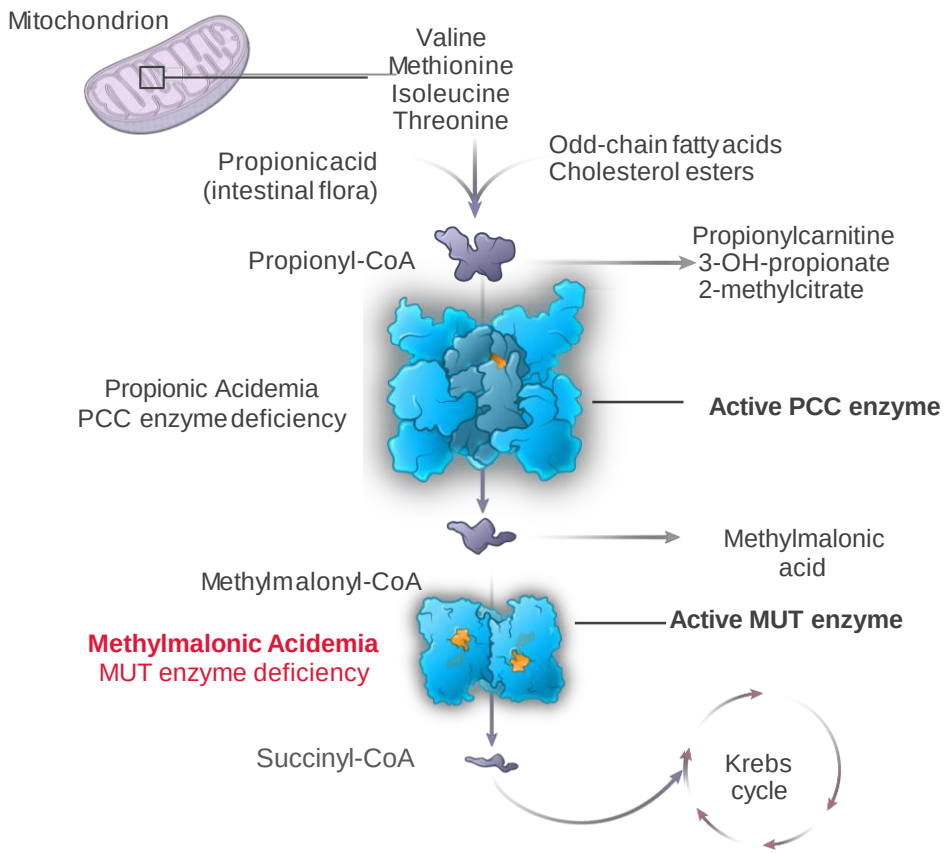
Overview of Methylmalonic Acidemia (MMA) due to MUT deficiency

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* causes 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

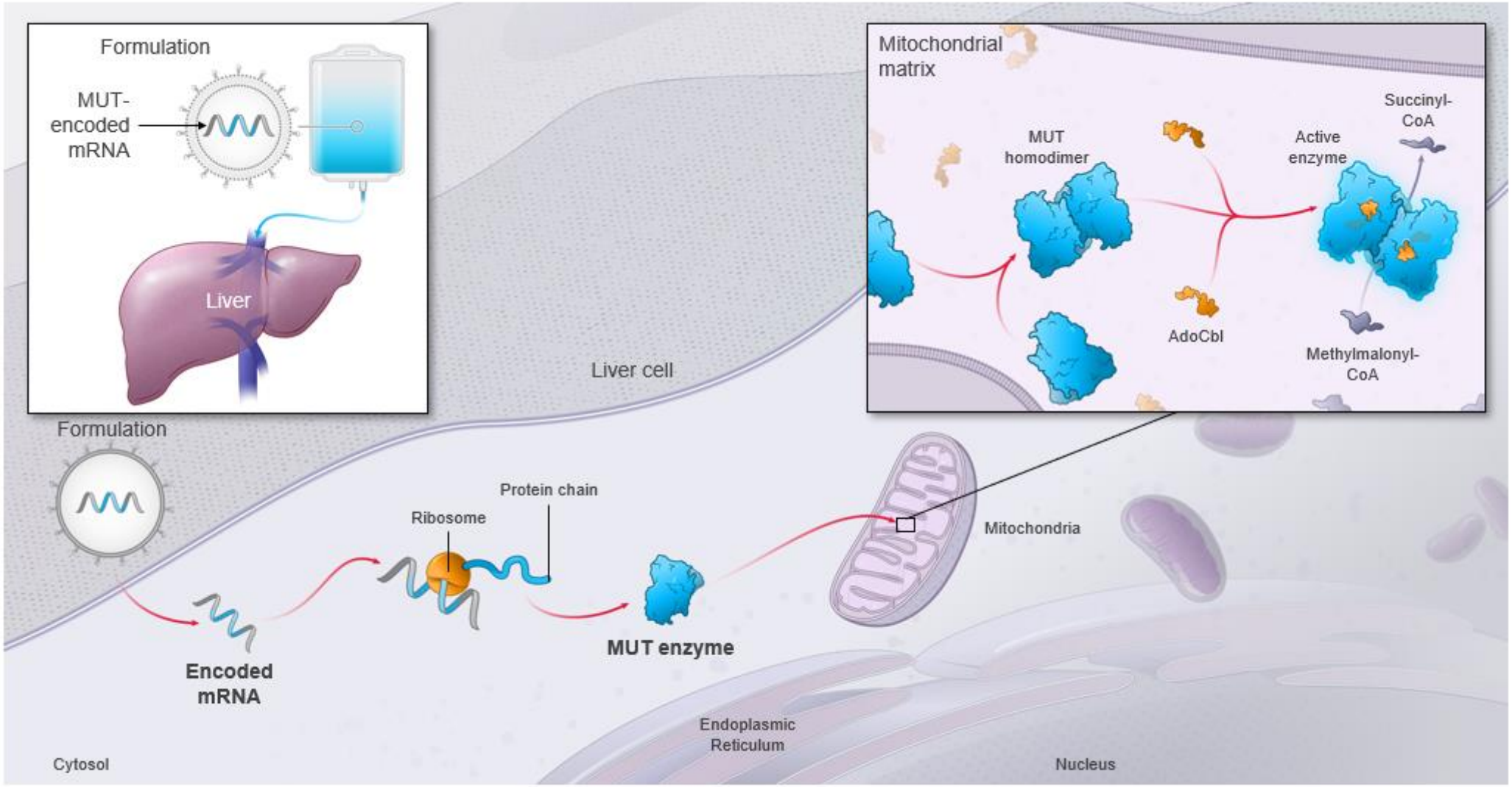
Current interventions include:

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

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

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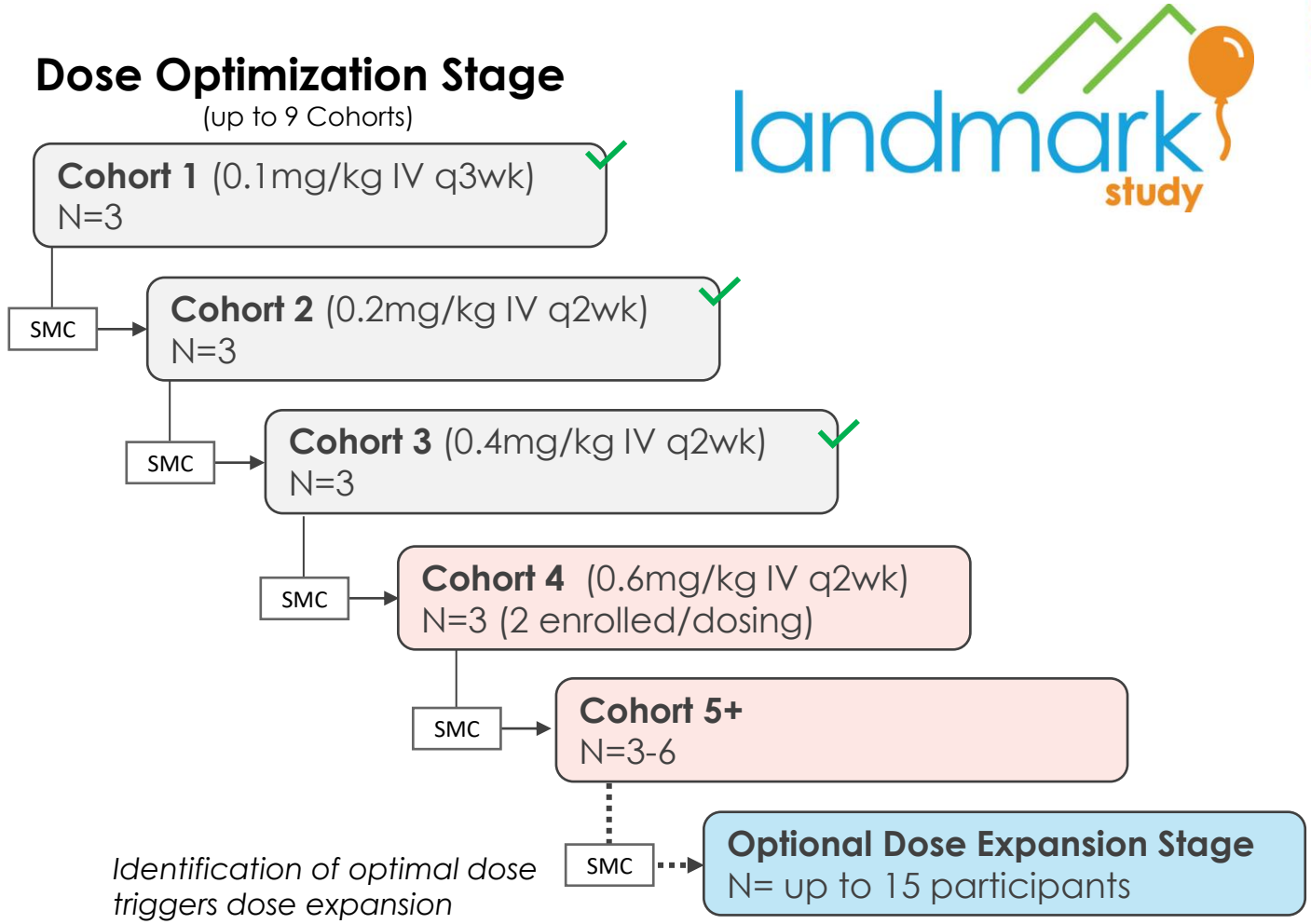
Ongoing Phase 1/2 Study designed to evaluate safety and pharmacology of mRNA-3705 in participants with MMA

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



SMC: safety monitoring committee
✓: Fully enrolled

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

	Cohort 1 0.1 mg/kg Q3W (N=3)	Cohort 2 0.2 mg/kg Q2W (N=3)	Cohort 3 0.4 mg/kg Q2W (N=3)	Cohort 4 0.6 mg/kg Q2W (N=2)	Total (N=11)
Age at enrollment, median (years)	12.17	2.67	7.83	11.54	7.83
Min, Max	4.5, 14.4	2.5, 39.5	5.8, 16.0	4.3, 18.8	2.5, 39.5
Age at disease onset, median (months)	0	0	3	58.5	0
Min, Max	0	0, 1	0, 10	0, 117	0, 117
Sex, n					
Male	1	1	1	2	5
Female	2	2	2	0	6
Weight					
Weight at baseline, median (kg)	25.70	13.40	22.50	38.55	22.50
Min, Max	19.5, 41.4	12.3, 58.0	16.6, 54.9	16.5, 60.6	12.3, 60.6
Phenotype					
Mut0	3	3	3	1	10
Mut-	0	0	0	1	1

mRNA-3705-P101: clinical experience to date

As of August 25, 2023*:

- Eleven participants have been dosed, with a total of 221 doses administered
- Total cumulative treatment duration among all participants is ~10.5 patient-years
  - Median treatment duration among all participants is 1.02 patient-years
  - Maximum participant treatment duration is 1.95 patient-years
- Study is ongoing; final participant in Cohort 4 expected to be enrolled soon
- 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

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

Safety in mRNA-3705-P101: overall Summary to date

As of August 25, 2023:

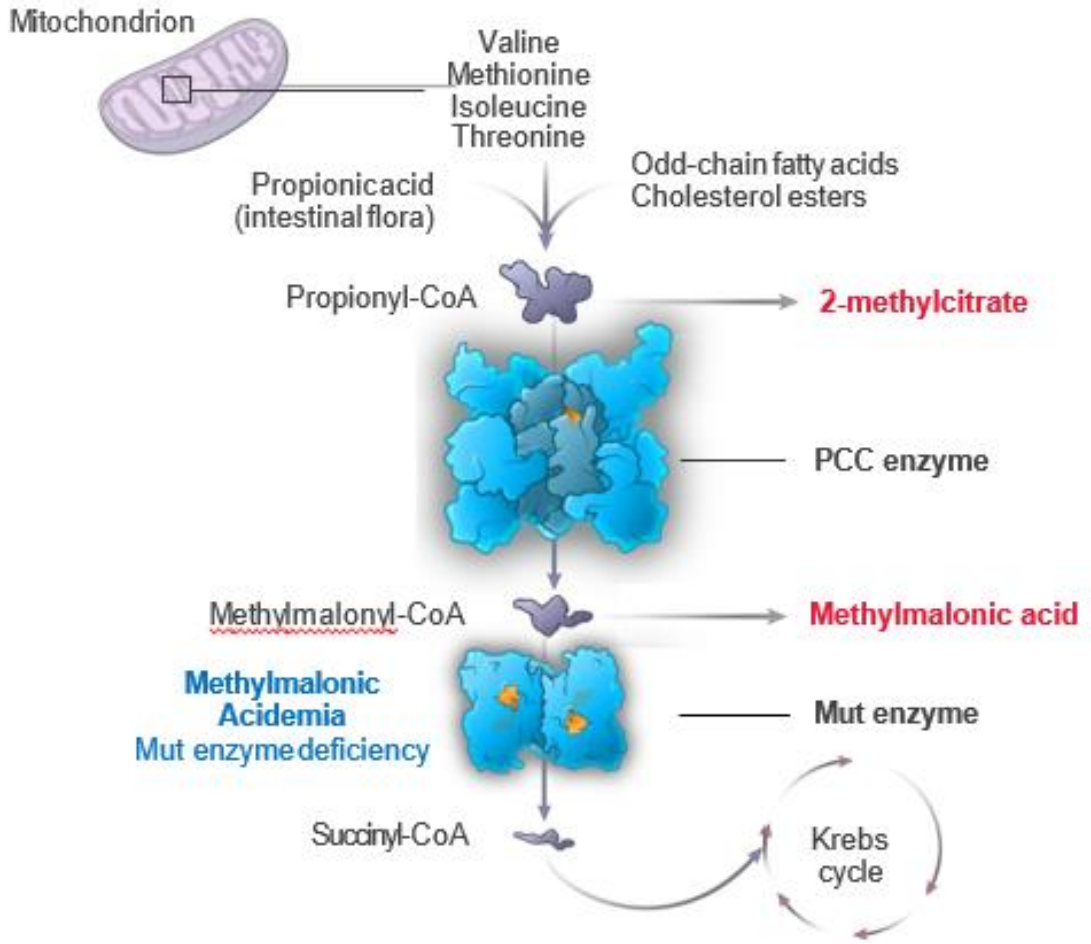
- No deaths or discontinuations due to safety-related reasons
  - One discontinuation in the extension for non-safety reasons
- No events meeting dose-limiting toxicity criteria have been observed
- 1 Serious AE assessed as related to mRNA-3705 by the Investigator:
  - Event of "body temperature increased" (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 adverse events (AEs) are pyrexia (n=4) and upper respiratory tract infection (n=4)
- 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

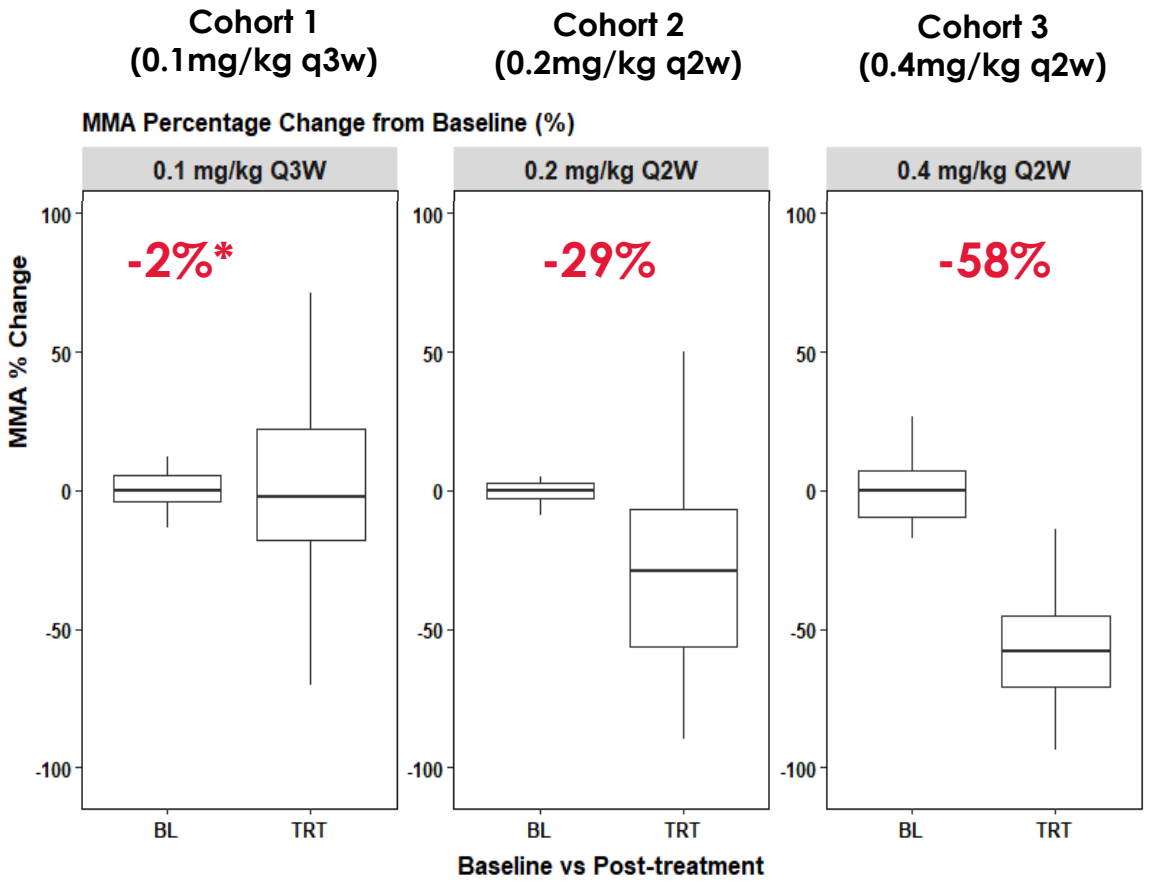
Changes in concentrations of methylmalonic acid generally **correlate with disease severity** and natural history data suggest that changes in methylmalonic acid may be associated with clinical events

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

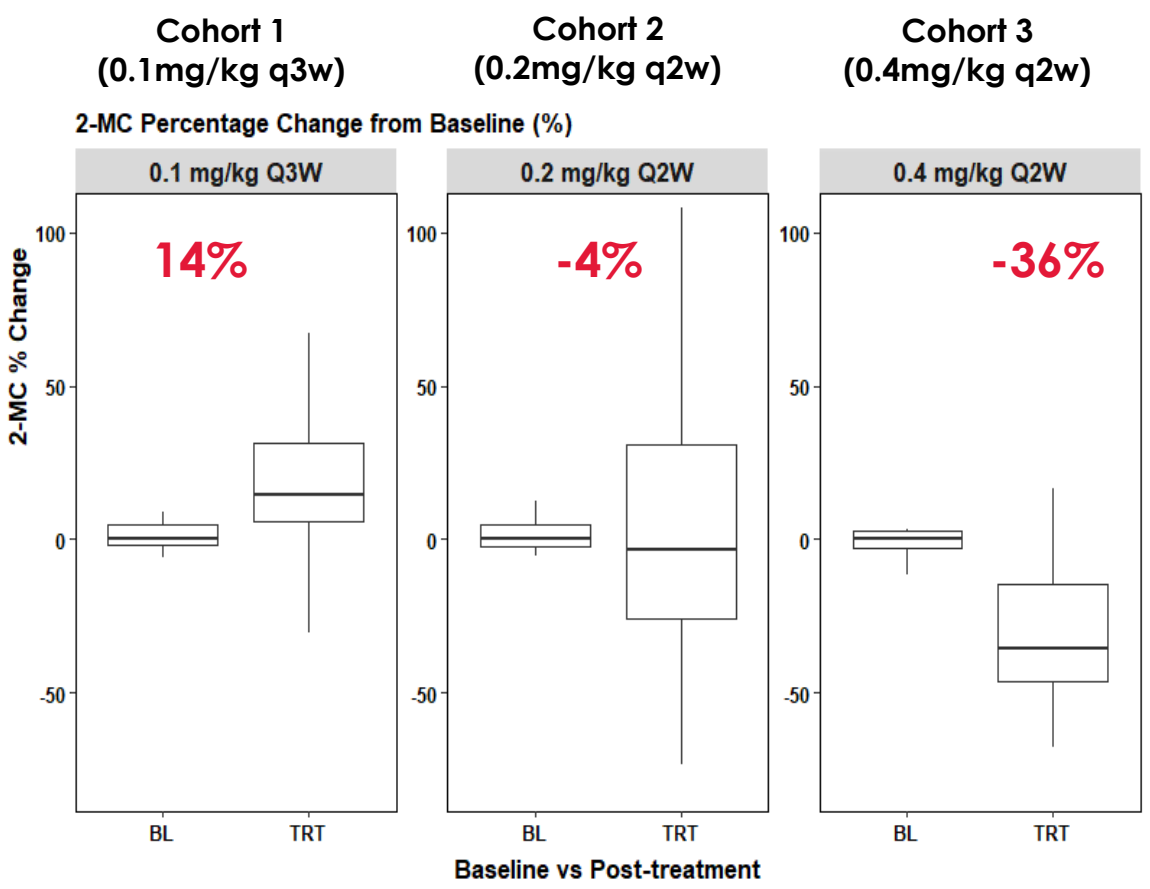


mRNA-3705-P101: dose-dependent changes in key biomarkers

Methylmalonic Acid



2-Methylcitrate



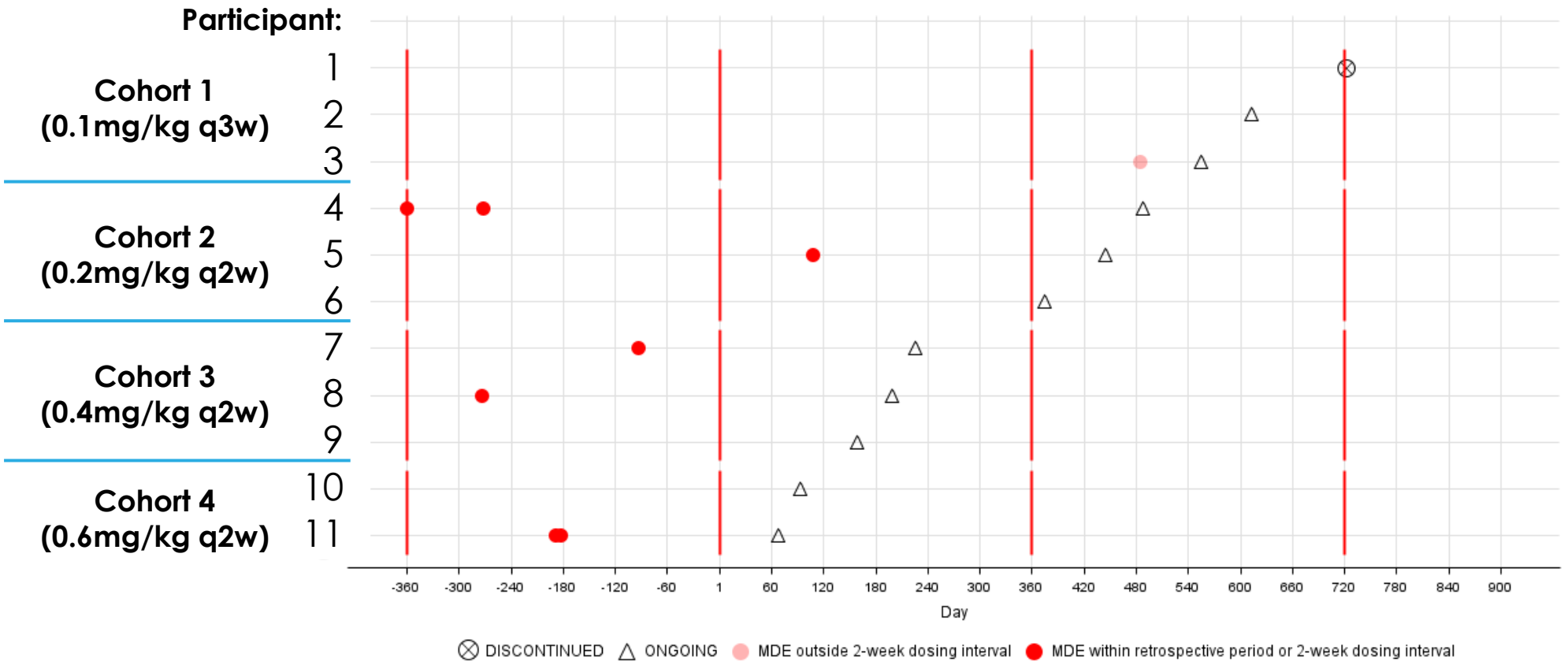
*Overall percent change from pre-treatment median baseline is shown for each cohort

Cohort 4 Update

As of September 13, 2023:

- Recently initiated dosing in cohort 4, two patients enrolled, small number of doses per patient
- Safety and tolerability consistent with prior cohorts but continuing to follow
- The cohort includes the first patient with a Mut $^{-}$
- We've not yet observed decreases in the MMA levels, however it is early in the course of their treatment
- We will continue to enroll in this cohort and make a determination on further dose escalation

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



Comparing pre- to post-treatment, initial data:
To date no MDEs observed at expected efficacious dose levels (0.4mg/kg and above)

Data as of 25Aug2023

Summary

As of September 13, 2023:

- **Expanding clinical experience:** Cumulative treatment duration of over 10.5 patient years
- **Safety:** Generally well-tolerated to date with no discontinuations due to safety and no events meeting protocol-defined dose-limiting toxicity criteria
- **Encouraging initial pharmacodynamic data:** Dose-dependent reductions in methylmalonic acid in Cohorts 2 and 3
- **Clinical endpoints:** Early results suggest potential decreases in annualized MDE frequency and MMA-related hospitalizations compared to pre-treatment
- **Next steps:** Expecting to advance program into registrational studies in 2024

Forward-looking statements

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 to advance mRNA-3705 into registrational studies in 2024. 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.