P-521

Model-Informed Dose Selection for the Pivotal Study of mRNA-3705 in Methylmalonic Acidemia

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BACKGROUND

- Methylmalonic acidemia (MMA) is a rare inherited metabolic disorder primarily caused by a deficiency in the methylmalonyl-CoA mutase (MUT) enzyme, with onset typically at birth or early infancy[1,2]
  - Patients with MUT-deficient MMA can be categorized based on residual MUT activity as mut^0 (no activity) or mut$^-$ (reduced activity)[1,2]
  - MMA is associated with high mortality and morbidity and is characterized by potentially life-threatening metabolic decompensation events[1,2]
- Deficiency of the MUT enzyme results in an accumulation of toxic metabolites, including methylmalonic acid, 2-methylcitrate (2-MC), 3-hydroxypropionic acid (3-HP), and propionylglycine (n-PG)[1,3]
  - Measuring levels of these metabolites may serve as biomarkers for disease progression in patients with MMA[4]
- mRNA-3705 is an investigational, lipid nanoparticle–encapsulated therapy administered intravenously that codes for the human MUT (hMUT) enzyme and is hypothesized to restore normal MUT production[5]
- The ongoing, phase 1/2, multicenter, 3-part mRNA-3705-P101 study is evaluating mRNA-3705 in participants with MUT-deficient MMA
  - We present pharmacokinetic and pharmacodynamic findings from Part 1 of the study, along with analysis from a population pharmacokinetic/pharmacodynamic model

OBJECTIVES

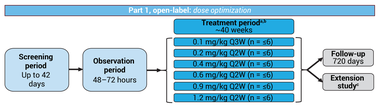
- To select the optimal dose of mRNA-3705 in participants with MUT-deficient MMA using mRNA pharmacodynamic and biomarker data from the mRNA-3705-P101 study

METHODS

Study Design, Participants, and Treatment

- An ongoing, multicenter, 3-part, phase 1/2 study of mRNA-3705 in participants with MUT-deficient MMA (NCT04899310)
  - After the primary study, participants can enroll in the phase 1/2, open-label mRNA-3705-P101-EXT extension study (NCT05295433)

Figure 1. Phase 1/2 mRNA-3705-P101 study design: part 1



Q2W, every 2 weeks; Q3W, every 3 weeks.
[a]mRNA-3705 is administered intravenously for ≤10 doses.
[b]14-day dose-limiting window after dose 1 for each participant.
[c]Participants enrolled in the extension study receive the same dose of mRNA-3705 as they received in part 1.

Table 1. Eligibility Criteria

Key Inclusion Criteria	Key Exclusion Criteria
• Isolated MMA due to MUT deficiency confirmed by molecular genetic testing • ≥1 yr of age • Body weight of ≥11.0 kg • Blood vitamin B12 level ≥lower limit of normal	• Isolated MMA cb1A, cb1B, or cb1D enzymatic subtypes, or methylmalonyl-CoA epimerase deficiency, or combined MMA with homocystinuria • Laboratory abnormalities achieving exclusionary thresholds • eGFR <30 mL/min/1.73 m^2 or chronic dialysis • QTc >480 msec using Bazett's correction • Previously received gene therapy for the treatment of MMA • Positive pregnancy test or pregnant or breastfeeding • History of or planned organ transplant • Underwent major surgery ≤30 d before screening

eGFR, estimated glomerular filtration rate; QTc, corrected QT interval.

Endpoints

- The primary endpoint for part 1 was safety and tolerability of mRNA-3705
- Key secondary endpoints included
  - Percentage change in plasma methylmalonic acid and 2-MC levels from baseline after 1 dose and after repeated administration of mRNA-3705
  - Estimation of hMUT mRNA pharmacokinetic parameters
- Key exploratory endpoints included
  - Percentage change in levels of other disease-related biomarkers from baseline, including 3-HP and n-PG

Statistical Analysis

- Pharmacodynamic and pharmacokinetic parameters were assessed in all participants who received ≥1 dose of mRNA-3705 and had ≥1 evaluable posttreatment biomarker and hMUT mRNA concentration, respectively
- Baseline plasma biomarker levels were calculated based on the median value from available biomarker levels obtained during the observation period and the dose 1 pre-infusion level
  - Changes from baseline in median biomarker levels over time were summarized descriptively
- Blood hMUT mRNA levels were summarized descriptively

Population Pharmacokinetic/Pharmacodynamic Modeling Analysis

- A population pharmacokinetic/pharmacodynamic model was developed using mRNA pharmacokinetic (hMUT mRNA exposure), biomarker (plasma methylmalonic acid levels), and clinical data (alanine transaminase/aspartate aminotransferase correlation) from part 1 of the study
  - Data incorporated in the model were stratified by age based on clinical and pharmacokinetic/pharmacodynamic results from part 1 of the study (all ages vs ≥5 years) and phenotype (mut^0 vs mut$^-$) across dose cohorts
- Exposure-response relationships were evaluated using E_max models in participants with mut^0 MMA

RESULTS

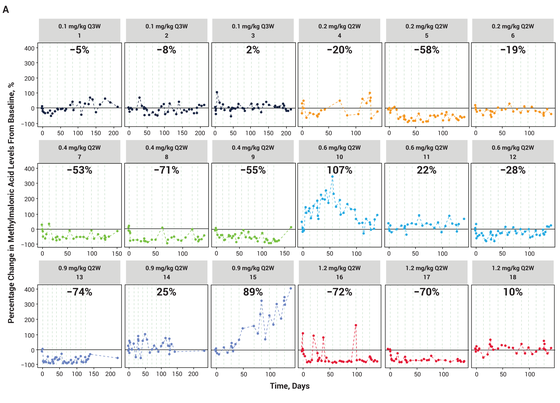
Participants

- At the data cutoff date (July 31, 2025), 18 participants were enrolled in part 1 and received treatment with mRNA-3705 at doses of 0.1 mg/kg Q3W, 0.2 mg/kg Q2W, 0.4 mg/kg Q2W, 0.6 mg/kg Q2W, 0.9 mg/kg Q2W, and 1.2 mg/kg Q2W (n = 3 in each dose cohort)

Pharmacodynamic Response

- In Part 1, a dose-dependent reduction in plasma methylmalonic acid levels from baseline was observed, with ≥50% reductions in half of the participants treated with mRNA-3705 ≥0.4 mg/kg Q2W (**Figure 2**)
  - Reductions were generally greater in participants aged ≥5 years with mut^0 MMA vs mut$^-$ MMA and <5 years of age (**Figure 3**)
- Incremental reductions in methylmalonic acid levels were observed in 1 participant following mRNA-3705 dose escalation from 0.4 mg/kg in Part 1 to 0.9 mg/kg then 1.2 mg/kg in the extension study (**Figure 4**)
- In Part 1, reductions in other disease-related biomarkers (2-MC, 3-HP, and n-PG) were observed in all participants who also had reductions in methylmalonic acid levels ≥25% (**Table 2**)

Figure 2. (A) Percentage Change From Baseline in Plasma Methylmalonic Acid Levels and (B) Absolute Plasma Methylmalonic Acid Concentrations Over Time in Individual Participants in Part 1



In both panels, data are shown for all 18 participants (participant 1–18). In panel A, the median percentage change from baseline values are shown in black text. Vertical dashed green lines represent doses administered. In panel B, the horizontal unbroken black lines represent the baseline methylmalonic acid level, the horizontal dashed black lines represent methylmalonic acid levels of 400 µM, and vertical dashed green lines represent doses administered.

Figure 3. Percentage Change From Baseline in Plasma Methylmalonic Acid Levels (A) Over Time by Dose, Phenotype, and Age, and (B) After First Dose of mRNA-3705 by Dose and Phenotype for all Participants in Part 1

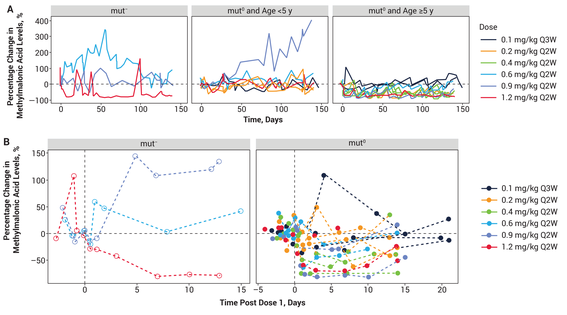
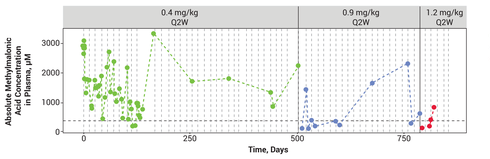


Figure 4. Absolute Plasma Methylmalonic Acid Concentrations After mRNA-3705 Dose Escalation in 1 Participant in Part 1 and the Extension study[a]



The horizontal dashed black line represents methylmalonic acid levels of 400 µM, the vertical unbroken black lines represent dose escalations, and the vertical dashed grey lines represent doses administered.
[a]The dose of mRNA-3705 was escalated in 1 participant (participant 5) from 0.4 mg/kg Q2W in Part 1 to 0.9 mg/kg Q2W then 1.2 mg/kg Q2W in the extension study.

Table 2. Percentage Change From Baseline in Other Disease-Related Biomarkers in Part 1

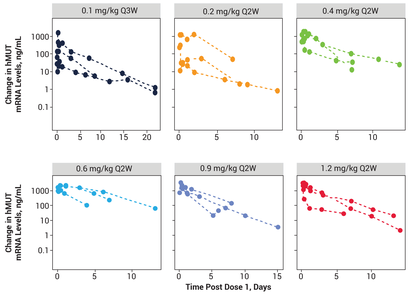
Dose	Participant	Phenotype	Methylmalonic acid reduction, median, %	2-MC reduction, median, %	3-HP reduction, median, %	n-PG reduction, median, %
0.1 mg/kg Q3W	1	mut^0	−5	26	3	51
	2	mut^0	−8	10	NA	NA
	3	mut^0	2	17	−9	39
0.2 mg/kg Q2W	4	mut^0	−20	31	NA	NA
	5	mut^0	−58	−28	−32	−33
	6	mut^0	−19	22	NA	NA
0.4 mg/kg Q2W	7	mut^0	−53	−39	−26	−32
	8	mut^0	−71	−46	−45	−73
	9	mut^0	−55	−18	−37	−43
0.6 mg/kg Q2W	10	mut$^-$	107	38	14	−7
	11	mut^0	22	3	39	4
	12	mut^0	−28	−20	−12	−34
0.9 mg/kg Q2W	13	mut^0	−74	−51	−47	−67
	14	mut$^-$	25	3	11	28
	15	mut^0	89	52	NA	NA
1.2 mg/kg Q2W	16	mut$^-$	−72	−37	−56	−47
	17	mut^0	−70	−52	−64	−75
	18	mut^0	10	−9	NA	NA

NA, not assessable.

Pharmacokinetic Response

- In Part 1, hMUT mRNA exposure was dose-dependent (**Figure 5**)

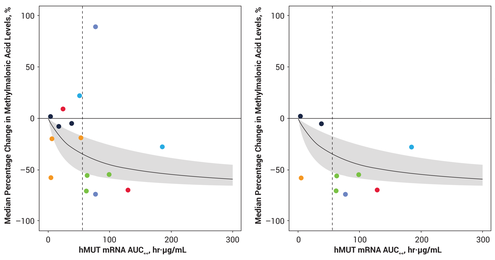
Figure 5. The Pharmacokinetic Profile of hMUT mRNA After First Dose of mRNA-3705 by Dose in all Participants in Part 1



Exposure Response

- Exposure-response analyses included data from participants with mut^0 MMA in Part 1 (n = 15)
- The model estimated an EC_{50} of 55 hr·µg/mL (**Figure 6**)
  - A dose of 1.2 mg/kg is predicted to achieve hMUT mRNA exposure above the EC_{50} threshold and is consistent with the ≥50% reduction in methylmalonic acid levels from baseline observed at this dose

Figure 6. Exposure-Response Analysis of Median Methylmalonic Acid Percentage Change From Baseline by Dose in (A) Participants With mut^0 MMA and (B) Participants Aged ≥5 Years With mut^0 MMA in Part 1



AUC$_{ss}$, area under the curve at steady-state.
Vertical dashed lines represent estimated EC_{50} values from the E_max model. The shaded area represents the 90% CI for the E_max model prediction.

CONCLUSIONS

- In this analysis of MUT-deficient MMA, mRNA-3705 resulted in dose-dependent reductions in levels of methylmalonic acid and other disease-related biomarkers, indicating a dose-dependent effect of mRNA-3705
  - In Part 1, reductions in biomarker levels were most pronounced in participants with mut^0 MMA aged ≥5 years
  - Incremental reductions in methylmalonic acid levels were observed after mRNA-3705 dose escalation from 0.4 mg/kg to 0.9 mg/kg then 1.2 mg/kg in the extension study
- Target exposure and biomarker response were achieved with an mRNA-3705 dose of 1.2 mg/kg Q2W
  - Interim clinical findings demonstrated a manageable safety profile of mRNA-3705, with no dose-limiting toxicities or treatment-emergent adverse events leading to treatment discontinuation (Oral Presentation #8 [mRNA-3705 Therapy for Methylmalonic Acidemia: Interim Data From a Phase 1/2 Study])
- Based on the totality of evidence, a dose of 1.2 mg/kg mRNA-3705 Q2W was selected for further clinical evaluation in the pivotal study (Part 2)

References

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Acknowledgements

The authors thank the participants and their families and all investigators and site personnel who participated in this study. This study (ClinicalTrials.gov Identifier, NCT04899310; NCT05295433) was sponsored by Moderna, Inc, Cambridge, MA, USA. Medical writing assistance was provided by Aisling Towell, PhD, of ICON plc (Blue Bell, PA, USA). This assistance was funded by Moderna, Inc.

Disclosures

ML, MZ, RP, TH, JP, EL, JK, DC, PVR, CW, and WG are employees of and stockholders in Moderna, Inc. HL has nothing to disclose.

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Scan here for a digital version of oral presentation #8 (mRNA-3705 Therapy for Methylmalonic Acidemia: Interim Data From a Phase 1/2 Study).

Presented at the International Congress of Inborn Errors of Metabolism (ICIEM), Kyoto, Japan; September 2–6, 2025