Safety and Tolerability of Single and Repeat Doses of MRT5005, an Inhaled CFTR mRNA Replacement Therapy, in Adult CF Patients

Poster # 544

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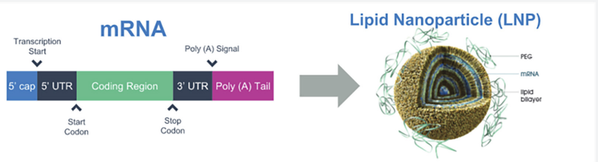
Introduction

- Despite the high efficacy of modulator therapy, not all patients with CF respond to modulators, and roughly 10% of patients with CF carry mutations for which modulator therapy is not indicated.
- Messenger RNA (mRNA) therapy represents a novel approach for treating all patients with CF lung disease, regardless of genotype.
- MRT5005 is a codon-optimized messenger RNA (mRNA) therapeutic coding for the human cystic fibrosis transmembrane regulator (CFTR) protein, formulated in lipid nanoparticles (LNPs) suitable for nebulization (**Figure 1**).[1]
- RESTORE-CF (www.clinicaltrials.gov, NCT03375047) is a double-blind, placebo-controlled Phase 1/2 clinical trial conducted in the United States in adult CF patients that aims to evaluate the safety and tolerability of single, weekly, and daily doses of inhaled MRT5005.
- Here, we report interim results of RESTORE-CF patients up to 1 month after either a single dose or the last of 5 doses of MRT5005 or placebo.

Figure 1. mRNA Structure and LNP



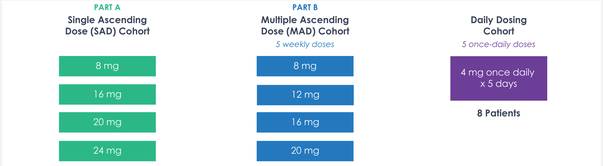
Methods

Study Design

- The design and methodology of RESTORE-CF have been described previously.[2]
- Forty-two adult CF patients were randomized 3:1 to receive nebulized MRT5005 or placebo (normal saline) in a clinic setting as follows (**Figure 2**):
  - Single Ascending Dose (SAD) cohort: single doses of 8mg, 16mg, 20mg, 24mg or placebo
  - Multiple Ascending Dose (MAD) cohort: 5 weekly doses of 8mg, 12mg, 16mg, 20mg, or placebo
  - Daily Dosing cohort: 5 consecutive daily doses of 4mg or placebo
- Patients with $ppFEV_1$ ≥50% and ≤90% and two Class I and/or Class II CFTR mutations were eligible for inclusion in the study.
  - In SAD and MAD cohorts, concomitant treatment with lumacaftor/ivacaftor or tezacaftor/ivacaftor was permitted (stable regimen for at least 28 days prior to screening visit).
  - Daily Dosing cohort patients were permitted to be concomitantly treated with lumacaftor/ivacaftor, tezacaftor/ivacaftor, or elexacaftor/tezacaftor/ivacaftor.
- MRT5005 was administered 2-3 hours after routine pulmonary therapies.
  - For patients whose pulmonary medications did not include an inhaled short-acting beta-agonist, albuterol (2 to 4 puffs) was administered approximately 20 minutes before MRT5005.
- Patients were followed for at least 1 month after the final dose[a] before unblinding and analysis.
- Assessments included adverse events, blood samples for mRNA and lipid quantitation, immunogenicity testing, spirometry, electrocardiogram (ECG), and clinical safety labs.

a The 1 month post-dose time interval is defined as through Day 29 for SAD, Day 57 for MAD, and Day 32 for Daily Dosing cohort.

Figure 2. RESTORE-CF Study Design



Results

Patient Disposition

- Of the 53 patients screened, 42 were enrolled and randomized to receive MRT5005 (n=31) or placebo (n=11).
- Four patients discontinued treatment:
  - Three patients receiving MRT5005 (two due to adverse events (febrile reaction, hypersensitivity reaction), one due to COVID-related risks of continuing clinic visits for this study)
  - One patient receiving placebo (COVID-related risks of continuing clinic visits for this study)
- One additional patient was assigned to a single dose of MRT5005 and withdrew due to pregnancy 147 days after receiving the single dose.

Figure 3. Patient Disposition

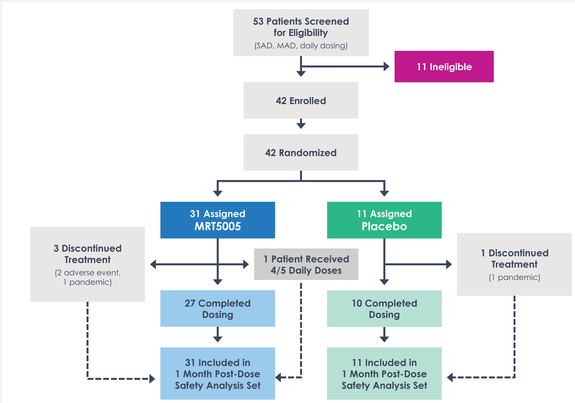


Table 1. Baseline Demographics

Characteristic	MRT5005 (n=31)	Placebo (n=11)
Age (mean, SD)	27.8 (7.41)	29.3 (13.27)
Sex, n (%) Female	17 (54.8)	6 (54.5)
Race, n (%) White Black or African-American	31 (100) 0	10 (90.9) 1 (9.1)
Genotype Class I/Class I Class I/Class II Class II/Class II Class II/Undetermined[a]	2 (6.5) 8 (25.8) 20 (64.5) 1 (3.2)	3 (27.3) 5 (45.4) 3 (27.3) 0
CFTR modulator use at baseline, n(%)	19 (61.3)	8 (72.7)
Percent predicted FEV_1 at baseline, n(%)[b] < 70 ≥ 70	20 (64.5) 11 (35.5)	7 (63.6) 4 (36.4)

a F508del/Q452P mutation.
b Baseline value was defined as the average of the results from testing on Day -1 and at pre-dose on Day 1; Daily Dosing cohort baseline $ppFEV_1$ based on pre-dose Day 1 only.

Safety Summary

- Majority of TEAEs were mild or moderate in severity.
- The most common TEAEs in the MRT5005 cohorts were cough and headache (29 and 26 total events, respectively).
- Two patients discontinued treatment due to TEAEs:
  - Febrile reaction (16mg MAD), hypersensitivity reaction (4mg Daily Dosing)
- No apparent trends in safety labs, vital signs, ECG, chest X-rays were observed.

Table 2. TEAE Summary (pooled cohorts)

TEAEs through 1 Month Post-Dose[a]	Pooled MRT5005 (n=31)		Pooled Placebo (n=11)	
Patients with any TEAE Mild, n (%) Moderate, n (%) Severe[b], n (%)	29 (93.5) 11 (35.5) 16 (51.6) 2 (6.5)		10 (90.9) 7 (63.6) 3 (27.3) 0	
Patients with serious TEAEs[c], n (%)	1 (3.2)		0	
Patients with TEAEs Leading to Discontinuation, n (%)	2 (6.5)		0	
Number of Events and Patients with TEAEs (at least 10 events in Pooled MRT5005 group)	**Events**	**Patients**	**Events**	**Patients**
TEAE Preferred Term[c] Cough Headache Pyrexia Chills Chest Discomfort Pulmonary Exacerbation Wheezing	29 26 15 14 11 10 10	16 16 9 10 4 9 6	3 2 0 0 1 1 2	2 2 0 0 1 1 2

a The 1-month post-dose time interval is defined as through Day 29 for SAD, Day 57 for MAD, and Day 32 for Daily Dosing Cohort.
b Pulmonary exacerbation (20mg SAD), myalgia upper back (20mg MAD).
c Pulmonary exacerbation (20mg SAD). dMRT5005 (n=29), Placebo (n=10).

Adverse Events of Special Interest

- Fourteen febrile reactions,[a] all mild or moderate in severity, were reported in 10/31 (32.3%) patients who received MRT5005, and none who received placebo (**Table 3**)
- Most occurred 3-14 hours after dosing and resolved within 24-48 hours with symptomatic treatment.[b]
- Similar reactions have also been observed in other trials with nucleic acid therapies encapsulated in LNPs.[3]
- Recurrence of febrile reaction was observed in 2 patients (both patients in MRT5005 20mg MAD cohort)
- One of these patients received premedication with ibuprofen 400mg, which appeared to mitigate symptoms.[c]
- Two patients who received MRT5005 experienced a hypersensitivity reaction,[d] both of which occurred within 24 hours of dosing, and resolved without sequelae:
- One patient in 20mg SAD cohort received symptomatic treatment, and one patient in 4mg Daily Dosing cohort discontinued treatment following the event.
- Neither of these hypersensitivity reactions met World Allergy Organization (WAO) definition of anaphylaxis.[4]

a Febrile reactions were identified based on a preferred term of body temperature increased or preferred term of pyrexia within the 24 hours after completion of nebulization on any dosing day with at least one other systemic symptom reported as a preferred term of headache, arthralgia, myalgia, fatigue, chills, nausea, or vomiting within the 24 hours after completion of nebulization on any dosing day.
b Symptomatic treatments included acetaminophen, ibuprofen, and ondansetron.
c Ibuprofen 400mg was also administered during nebulization of 5th dose in this patient.
d Hypersensitivity reactions were identified based on a preferred term of hypersensitivity within the 24 hours after completion of nebulization on any dosing day.

Table 3. Febrile and Hypersensitivity Reactions (MRT5005 Patients)

Each dot o denotes a dose of study medication completed by subject: ● Febrile Reaction ● Hypersensitivity Reaction

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6[b]
Single Dose (SAD)						
8 mg	●	○	○			
16 mg	○	●	○			
20 mg	○	○	●			
24 mg	●	●	●			
Weekly Doses (MAD)						
8 mg	○ ○ ○ ○ ○	○ ○ ○ ○ ○	○ ○ ○ ○ ○			
12 mg	○ ○ ○ ○ ○	○ ○ ○ ○[a]	● ○ ○ ○ ○			
16 mg	○ ○ ○ ○ ○	● (Early d/c)	● ○ ○ ○ ○	○ ○ ○ ○ ○		
20 mg	○ ○ ○ ○ ○	○ ○ ○ ○ ○	● ● ● ○ ●	● ● ○ ○ ○		
Daily Doses						
4 mg	○ ○ ○ ○ ○	○ ○ ○ ○ ○	○ ○ ○ ○ ○	○ ○ ○ ○ ○	○ ○ ● (Early d/c)	○ ○ ○ ○

a Early treatment discontinuation due to pandemic.
b Subject 6 completed 4/5 days of dosing; one missed due to inclement weather.

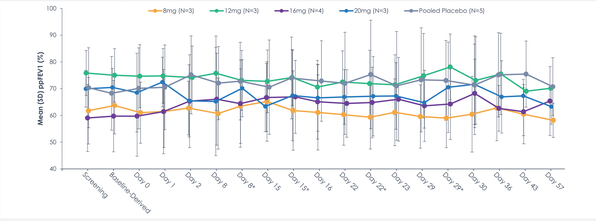
Pharmacokinetics and Immunogenicity

- mRNA and/or lipid were detected occasionally and at low levels in 14 patients receiving MRT5005 across the SAD, MAD, and Daily Dosing cohorts.
  - No clear dose-dependency was observed, and there were no signs of accumulation in the MAD or Daily Dosing cohorts.
- No pattern of immunogenicity to CFTR or polyethylene glycol (PEG) was detected.
  - Anti-CFTR antibodies, anti-PEG antibodies, and CFTR-sensitized T cell activation were detected sporadically across the SAD, MAD, and Daily Dosing cohorts.
  - However, positive values were also observed in placebo patients and at baseline, indicating the need for improved assays.
- There was no relationship between febrile or hypersensitivity reactions and the presence of mRNA, lipid or immunogenicity parameters.

Spirometry

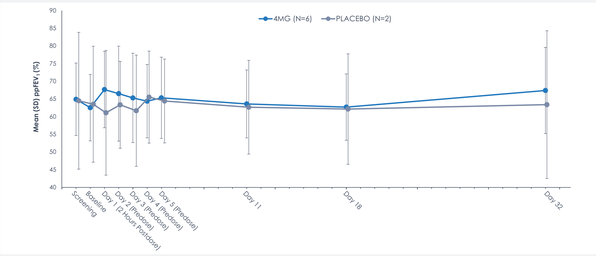
- Spirometry data from the SAD cohort have been described previously[1]; transient increases in $ppFEV_1$ were observed soon after dosing in some patients in the 16mg and 24mg but not in 8mg or 20mg group that followed the initial report.
- Data from patients in the MAD cohort were collected before and after dosing, and at 1, 2, and 4 weeks after the final dose; $ppFEV_1$ generally remained stable, and no clear increases/decreases in $ppFEV_1$ over time were observed (**Figure 4A**).
- Similarly, in the 4mg Daily Dosing cohort, $ppFEV_1$ measurements showed no clear trends over the dosing period (**Figure 4B**).

Figure 4A. Mean (SD) of Percent Predicted FEV1 Values by Dose Group and Visit Through Day 57 (MAD cohort)



* Post-dose assessments

Figure 4B. Mean (SD) of Percent Predicted FEV1 Values by Dose Group and Visit Through Day 32 (Daily Dosing cohort)



Conclusions

- RESTORE-CF, a Phase 1/2 trial evaluating the safety and tolerability of MRT5005, is the first clinical trial with an inhaled mRNA therapeutic.
- Repeat dosing of MRT5005 was generally safe and well-tolerated; majority of TEAEs were mild to moderate.
  - Self-limited febrile reactions occurred in some patients, as has been seen with other clinical trials evaluating LNP-encapsulated mRNA therapies.
  - Hypersensitivity reactions occurred in 2 patients; one received symptomatic treatment, and both resolved without sequelae.
- Detection of mRNA and/or lipid in the blood in some patients suggests successful delivery of inhaled mRNA.
- Presence of anti-CFTR, anti-PEG, or CFTR-sensitized T cell activation was detected in some patients (active and placebo cohorts, both before and after treatment), with no clear relationship to treatment or TEAEs.
- Measures of lung function remained relatively stable from baseline through 1 month of follow-up after the final dose.
- These findings will inform future development of MRT5005 and/or Next-Generation mRNA CF therapies.

References

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Acknowledgements

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