Safety and Tolerability of a Single Dose of MRT5005, a Nebulized CFTR mRNA Therapeutic, in Adult CF Patients

W17.6: Abstract # 515

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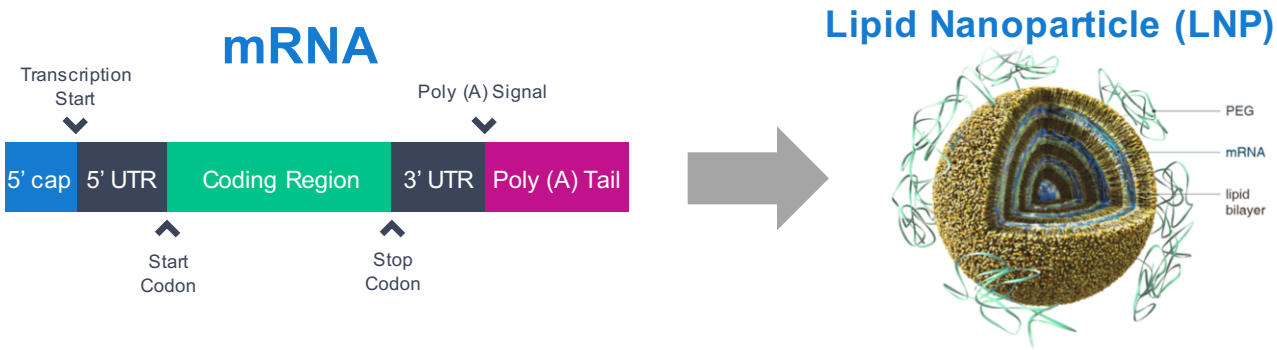
Disclosure slide for Dr. Zuckerman

- Scientific Advisory Board for Gilead Sciences

Introduction



- MRT5005 is a codon-optimized human CFTR mRNA, formulated in lipid nanoparticles (LNPs) suitable for nebulization.[1]
- It is designed to be a genotype-agnostic therapeutic addressing the underlying cause of cystic fibrosis (CF).
- RESTORE-CF, a Phase 1/2 clinical trial in adult patients with CF is ongoing in the USA (NCT03375047).
- Today, we report the results of the single-ascending dose (SAD) portion of the trial, comprising data through one month of follow-up after a nebulized dose of MRT5005 or placebo (saline).

[1]*Barbier et al., NACFC 2018*

RESTORE-CF: MRT5005 Phase 1/2 Clinical Trial Design

Design

- Randomized, double-blind, placebo-controlled, staggered dosing
- Each cohort: N=4 (3:1)

Objective

- Evaluate safety and tolerability of single and multiple escalating doses of MRT5005 administered by nebulization

Eligibility & Inclusion

- 18 years+
- ppFEV$_1$ ≥50% and ≤90%
- Patients with two Class I and/or Class II CFTR mutations

PART A:
Single Ascending Dose (SAD) Groups

8 mg → 16 mg → 24 mg

PART B:

Multiple Ascending Dose (MAD) Groups

5 weekly doses

Ongoing

12 Patients Total

MRT5005 Phase 1/2 SAD: Patient Demographics Overview

- The study enrolled 12 Caucasian subjects, 9 males, between 19-30 years of age.
- Of the 12 subjects, 11 had at least 1 F508del mutation, and 8 were F508del homozygotes (7 on stable regimen of lumacaftor/ivacaftor or tezacaftor/ivacaftor)
- One subject had no F508del mutation and was considered non-amenable to modulator treatment, including elexacaftor/tezacaftor/ivacaftor.

MRT5005 Phase 1/2 SAD: Results

MRT5005 Phase 1/2 SAD: Safety Overview

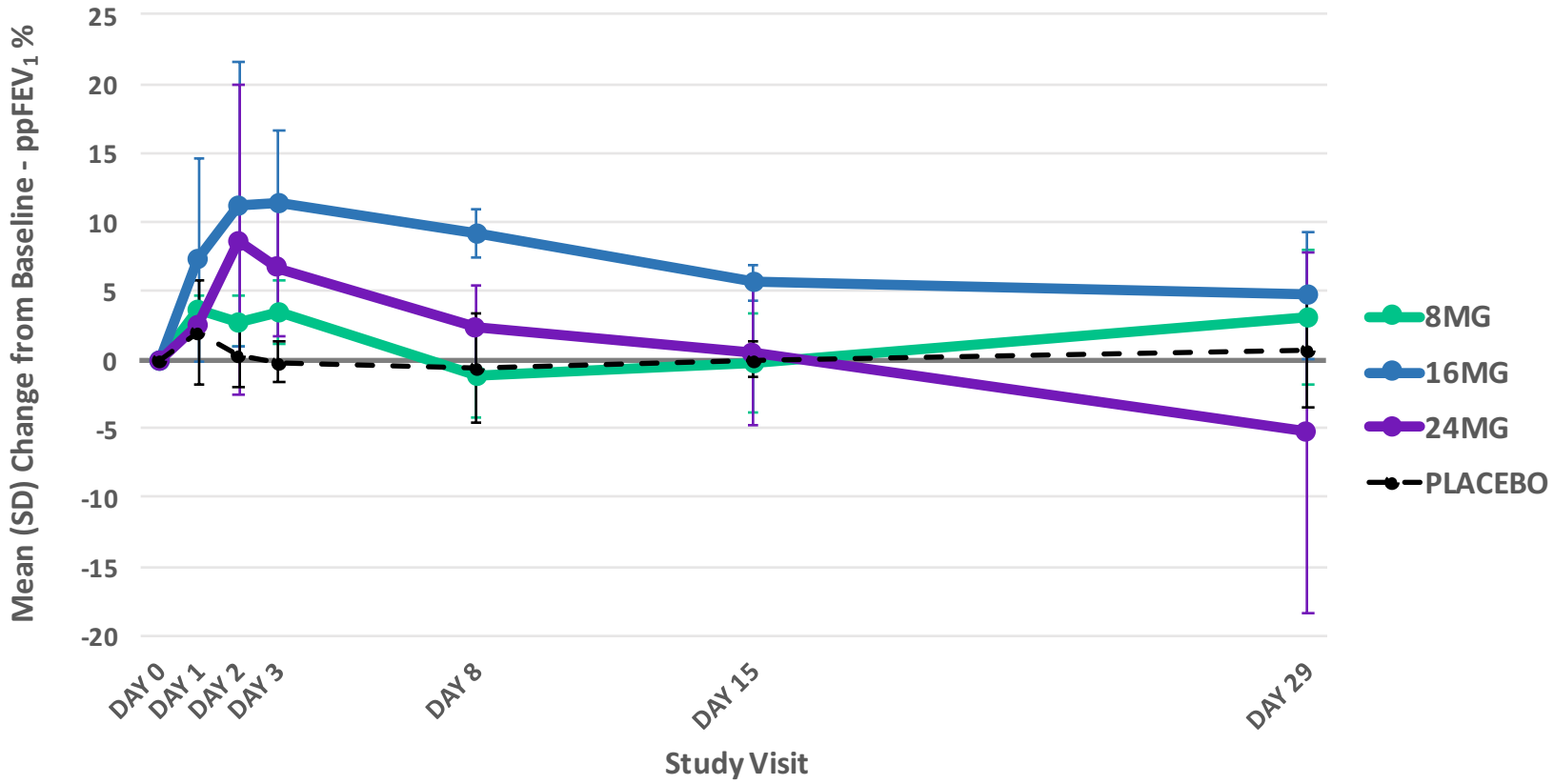
Treatment Emergent Adverse Events (TEAEs) through Day 29	Pooled Placebo (N=3)	MRT5005 8 mg (N=3)	MRT5005 16 mg (N=3)	MRT5005 24 mg (N=3)
Overall TEAEs	11	28	25	33
Not Related	9	11	9	10
Related	2	17	16	23
TEAEs by Severity				
Mild	11	23	24	21
Moderate	0	5	1	12
Severe	0	0	0	0
Serious TEAEs	0	0	0	0
TEAEs Leading to Discontinuation	0	0	0	0
TEAEs Resulting in Death	0	0	0	0
TEAEs Classified as Pulmonary Exacerbation	0	0	0	2*

** Occurred at Day 25 and Day 27*

MRT5005 Phase 1/2 SAD: $ppFEV_1$ Overview

- $ppFEV_1$ was measured at screening, Day -1, Day 1 (prior to dosing), 8 h after dosing, Day 2, Day 3, Day 8, Day 15 and Day 29.
- The average of the Day -1 and Day 1 (prior to dosing) value was considered as the Baseline value.
- Spirometry was performed using the TrueFlow™ Spirometer according to ATS/ERS2005 criteria and read by a central lab (Biomedical Systems)

MRT5005 Phase 1/2 SAD: Absolute Change in ppFEV$_1$ Over Time, Average Values



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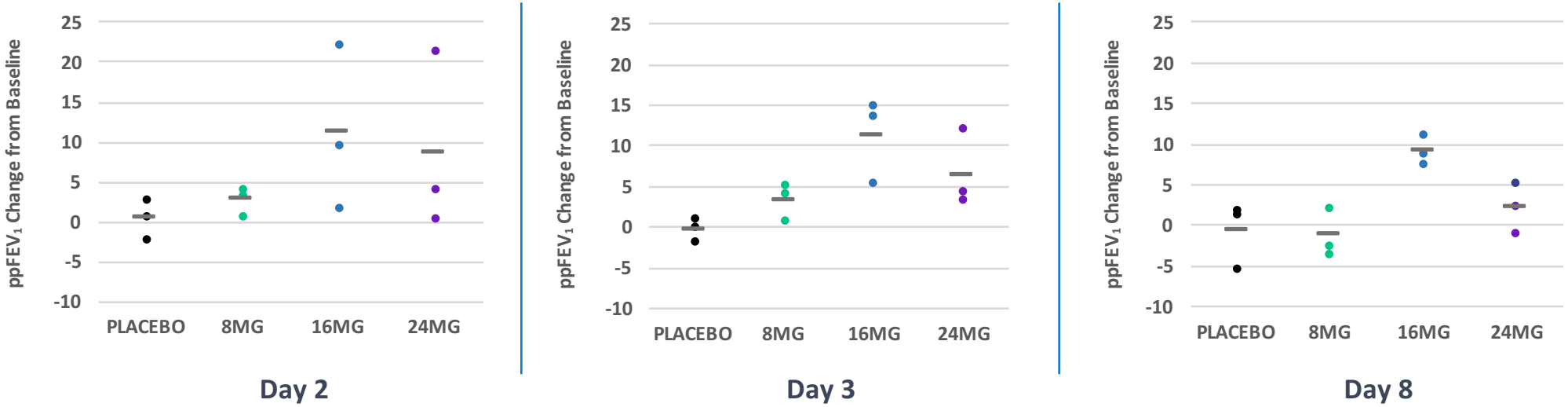
ppFEV$_1$ Change from Baseline – Days 2, 3 and 8



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MRT5005 Phase 1/2 SAD: Pharmacokinetics and Immunogenicity Data

Pharmacokinetic measurements were taken to evaluate mRNA and/or lipid in the blood

- Low levels of mRNA and/or lipid were detected in the blood of five subjects, 3 of whom were in the 24 mg dose group

Immunogenicity testing was performed using serum or whole blood in validated assays

- **Anti-drug antibodies:** *No anti-CFTR anti-drug antibodies detected*
- **T-Cell Response:** *No detection of T-cell sensitization*

MRT5005 Phase 1/2 SAD: Summary and Conclusions

- MRT5005, an inhaled, LNP-formulated mRNA therapy coding for the CFTR protein, was tested in a single-ascending dose study in 12 adult patients with CF.

- MRT5005 was generally well tolerated at the low- and mid-dose levels.
  - Mild to moderate febrile reactions were observed in 5 subjects receiving MRT5005, 3 of whom were in the 24 mg dose group. These reactions started approximately 4-10 hours after dosing and ended by 24 hours, allowing for discharge as planned.

- The observation that mRNA and/or lipid could be detected in the blood in some subjects indicates successful delivery of inhaled mRNA through the mucus.

- In 4/9 of the MRT5005 subjects, observed increases in $ppFEV_1$ within the 8 days after treatment were higher than expected based on known variability of $ppFEV_1$.

Acknowledgements

- Patients and investigators who participated in the RESTORE-CF clinical trial
- Cystic Fibrosis Foundation
- Translate Bio Bioanalytical team

Please see Poster #515 for additional detail!

Thank you

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