NCT Number: NCT03375047

CLINICAL STUDY PROTOCOL: MRT5005-101

TITLE:	A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled, Combined Single and Multiple Ascending Dose Study Evaluating the Safety, Tolerability, and Biological Activity of MRT5005 ([redacted]mRNA/[redacted] LNP) Administered by Nebulization to Adult Subjects with Cystic Fibrosis
DRUG:	MRT5005 ([redacted] [redacted]mRNA [[redacted]mRNA] complexed with [redacted] [redacted] lipid nanoparticle [[redacted]LNP])
IND:	IND 017747
EUDRACT NO.:	Non-EUDRACT
SPONSOR:	Translate Bio, Inc. 29 Hartwell Ave Lexington, MA 02421 USA
RESPONSIBLE PHYSICIAN:	[redacted] 29 Hartwell Ave Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 12 September 2017 Amendment 1: 18 January 2018 Amendment 2: 28 February 2019 Amendment 3: 29 July 2019 Amendment 4: 30 July 2020

COORDINATING INVESTIGATORS:

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PROTOCOL SIGNATURE PAGE

Sponsor's (Translate Bio) Approval:

[redacted]

Date

Chief Medical Officer
Translate Bio, Inc.
29 Hartwell Ave
Lexington, MA

INVESTIGATOR'S ACKNOWLEDGEMENT

I have read this protocol for Translate Bio Clinical Study MRT5005-101.

Title: A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled, Combined Single and Multiple Ascending Dose Study Evaluating the Safety, Tolerability, and Biological Activity of MRT5005 ([redacted] mRNA/[redacted] LNP) Administered by Nebulization to Adult Subjects with Cystic Fibrosis

Amendment/Version: Amendment 4, Version 5.0, dated 30 July 2020

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an Investigator for this study.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

MEDICAL MONITOR CONTACT INFORMATION

For protocol- or safety-related issues, the Investigator should contact the Medical Monitor. In the event of a fatal or life-threatening serious adverse event (SAE), the Investigator must contact the Medical Monitor immediately by phone. The SAE must also be entered into the electronic data capture (EDC) system as soon as possible to notify Rho Product Safety.

Medical Monitor:

[redacted]

Responsible Physician:

[redacted]

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ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATP	adenosine triphosphate
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CF	cystic fibrosis
CFR	Code of Federal Regulations
CFTR	cystic fibrosis transmembrane regulator
CRA	clinical research associate
CRF	case report form
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
[redacted]	
DMC	data monitoring committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practices
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
hCFTR	human cystic fibrosis transmembrane regulator

HCV	hepatitis C virus
HED	human equivalent dose
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
[redacted] LNP	[redacted]lipid nanoparticle
IP	investigational product
IRB	Institutional Review Board
Kg	kilogram
LNP	lipid nanoparticle
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
mL	milliliter
mRNA	messenger ribonucleic acid
NOAEL	no-observed-adverse-effect-level
PEG	polyethylene glycol
PSRC	Protocol Safety Review Committee
qPCR	quantitative polymerase chain reaction
rhDNase	recombinant human deoxyribonuclease I
RNA	ribonucleic acid
SAE	serious adverse event
µg	microgram
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia

STUDY SYNOPSIS

Name of Sponsor/Company:

Translate Bio, Inc.

Name of Investigational Product:

[redacted]mRNA [[redacted] mRNA] complexed with [redacted] lipid nanoparticle [[redacted] LNP] (MRT5005)

Name of Active Ingredient:

[redacted] messenger ribonucleic acid encoding for [redacted] (MRT5005 [redacted] mRNA)

Title of the study: A Phase 1/2, Randomized, Double-Blind, Placebo-Controlled, Combined Single and Multiple Ascending Dose Study Evaluating the Safety, Tolerability, and Biological Activity of MRT5005 ([redacted]mRNA/[redacted] LNP) Administered by Nebulization to Adult Subjects with Cystic Fibrosis

Study Center(s):

Multi-center in the US

Phase of Development: 1/2

Number of subjects (planned, total and for each treatment arm):

The study will be conducted at multiple centers in the US with expertise in treating cystic fibrosis (CF) patients. At least 40 male and female subjects with CF, 18 years of age or older, are planned to participate in the study. This will be a 3-part study with 16 subjects participating in Part A; 16 subjects participating in Part B; and 8 subjects participating in Part D. There will be an option to enroll and treat one additional group of subjects, with up to a maximum of 44 evaluable subjects participating in the study. Subjects will not be allowed to participate in more than 1 part of the study.

<u>Part A: Single Ascending Dose (SAD) Groups (N=16)</u>

In Part A, 4 groups consisting of 4 subjects each will be enrolled sequentially to receive single doses of nebulized MRT5005 (8, 16, 24, or 20 mg of [redacted] mRNA, the active drug substance of MRT5005 [nominal doses]) or placebo (normal saline). The 20 mg treatment group was added after blinded safety information from Group 3 revealed the occurrence of febrile reactions in 3 of 4 subjects. Within each dose group, subjects will be randomized in a 3:1 ratio to receive a single dose of either MRT5005 or placebo (3 subjects to receive MRT5005 and 1 subject to receive placebo per dose group).

<u>Part B: Multiple Ascending Dose (MAD) Groups (N=16)</u>

In Part B, 4 groups consisting of 4 subjects each will receive multiple doses of nebulized MRT5005 or placebo administered by nebulization. Three groups will be enrolled sequentially to receive dose levels of MRT5005 investigated as single doses in Part A (ie, 8 mg, 16 mg, and 20 mg). An additional dose level that was not investigated in Part A (ie, 12 mg) will also be evaluated in Part B. Within each dose group, subjects will be randomized in a 3:1 ratio to receive 5 doses of either MRT5005 or placebo (3 subjects to receive MRT5005 and 1 subject to receive placebo per dose group), administered 1 dose per week for 5 weeks.

Although 2 dose escalations are planned in both Parts A and B of the study, escalation to the next higher dose level may not occur if dose limiting toxicity is encountered at the current dose level.

Therefore, the number of subjects and groups required to complete the dose escalation sequences in either the SAD or MAD parts of the study may be less than planned.

If subjects do not complete the study or complete certain procedures, additional subjects will be enrolled at the Sponsor's discretion to ensure that at least 16, 16, and 8 evaluable subjects complete Parts A, B, and D of the study, respectively.

Part C (bronchoscopy groups) was removed from the protocol in the 3rd amendment to the protocol (Version 4.0 dated 29 July 2019).

Part D: Daily Dose Group (N=8)

In Part D, 8 subjects will be randomized in a 3:1 ratio to receive 5 consecutive daily doses of either 4 mg MRT5005 or placebo. Enrollment and treatment of subjects will not be staggered. Part D was added to the protocol (Version 5.0 dated 30 July 2020) to evaluate whether febrile reactions observed with higher doses (ranging from 8 mg to 24 mg) of MRT5005 are dose dependent or idiosyncratic. Investigation of a daily dosing regimen in Part D is attractive given the estimated short half-life of CFTR mRNA (14 hours) and translated CFTR protein (29 hours). The anticipated safety of 4 mg administered daily for 5 days (20 mg total) can be predicted from the safety and tolerability of 20 mg administered as a single dose in Part A.

Enrollment and Treatment of Additional Groups

A SAD dose group may be repeated in a new group of subjects in Part A to further assess the safety of the dose level before escalating to the next higher dose level, or before allowing it to proceed from Part A (SAD) to Part B (MAD).

It is expected that no more than 1 additional group of 4 subjects will be enrolled into the study. Therefore, up to a maximum of 44 evaluable subjects may participate in the study.

Principal/Coordinating Investigators: [redacted]

Objectives:

Primary

- The primary objective of the study is to evaluate the safety and tolerability of single and multiple escalating doses of MRT5005 administered by nebulization to adult subjects with CF.

Secondary

- The secondary objective of the study is to evaluate the effect on percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and other spirometry parameters after single and multiple escalating doses of MRT5005 administered by nebulization to adult subjects with CF.

Rationale:

Cystic fibrosis is an autosomal recessive genetic disorder that affects most critically the lungs, but also the pancreas, liver, and intestine. Cystic fibrosis is caused by a mutation in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which functions as a channel for transporting chloride across the plasma membrane. The CFTR protein is an important regulator of salt and water balance, and absent or decreased function of CFTR in the airway epithelium of CF patients results in thick, viscous secretions, which clog the airways and impair mucociliary clearance and other host defense mechanisms. This leads to chronic bacterial infection and inflammation of the lungs resulting in extensive damage and eventually respiratory failure. Lung disease is the major cause of morbidity and mortality in CF patients.

Messenger RNA (mRNA) therapy represents a new and novel approach for treating CF lung disease. In this therapeutic application, mRNA encoding for the wild-type CFTR protein is delivered directly by aerosol to the respiratory tract of CF patients resulting in the expression of normally functioning CFTR protein in the lungs. The efficient delivery and uptake of mRNA by bronchial epithelial cells is facilitated by formulation of the mRNA within cationic lipid-based nanoparticles. Following cellular uptake, translation of CFTR mRNA in the cytoplasm leads to the production of normal CFTR protein and restoration of CFTR chloride channel activity in the lungs.

This strategy was used to develop MRT5005, which utilizes an [redacted] lipid nanoparticle [redacted] LNP) as the vehicle to deliver [redacted] mRNA ([redacted] mRNA) to the lungs. [redacted] mRNA is the active drug substance of MRT5005. The primary component of the [redacted] LNP is the cationic lipid [redacted] which is mixed with two other non-cationic lipids, [redacted], to form the lipid nanoparticle (LNP). Complexation within the [redacted] LNP protects [redacted] mRNA from degradation and facilitates its aerosol delivery and uptake by the target bronchial epithelial cells in the lungs of CF patients.

Study MRT5005-101 represents an important first step in the evaluation of mRNA therapy as an approach to restoring CFTR function in the lungs of CF patients. The goal was to design a single study that could achieve both Phase 1 and 2 objectives while ensuring subject safety. This Phase 1/2, first-in-human study will evaluate the safety and tolerability of single and multiple escalating doses of MRT5005 administered by nebulization to the respiratory tract of adult subjects with CF.

Investigational Product, Dose, and Mode of Administration:

MRT5005 is a lipid nanoparticle suspension consisting of [redacted] mRNA ([redacted] mRNA), the active drug substance, formulated with the [redacted] lipids, [redacted] MRT5005 is dosed based on its content of [redacted] mRNA.

MRT5005 will be supplied as a sterile suspension in single-use vials. Each vial contains approximately 3.2 mL of MRT5005 at a concentration of 0.6 mg/mL of [redacted] mRNA. An InnoSpire Go nebulizer will be used to administer MRT5005 by nebulization at a flow rate of approximately 0.3 mL/minute. MRT5005 will be administered to subjects at the following 5 dose levels: 4, 8, 12, 16, 20, and 24 mg of [redacted] mRNA (nominal dose levels). The table below shows the volume of MRT5005 suspension to be nebulized and approximate nebulization time for each of the 5 dose levels of MRT5005 to be administered. As the medication cup of the InnoSpire Go holds only a maximum of 8 mL and will not be refilled during nebulization, multiple nebulizers may be used to administer the specified volume for each of the dose levels of MRT5005.

Sterile normal saline (Sodium Chloride Inhalation Solution, USP 0.9%) will be used as placebo. To maintain the blind of the study, the volume and nebulization time of placebo, and number of nebulizers used to deliver placebo will match that of the MRT5005 dosing group.

	Dosing of MRT5005 - Volumes and Nebulization Times					
	Dose of MRT5005 (mg)[a]					
	4	**8**	**12**	**16**	**20**	**24**
Total Nebulization Volume (mL)[b]	7	14	21	28	35	42
Nebulization Time (minutes)[c]	22	44	66	89	110	133
No. of Nebulizers[d]	1	2	3	4	5	6

[a] Nominal dose of [redacted] mRNA.

[b] Includes an additional 0.3 mL per each nebulizer to account for the expected residual volume after nebulization. Based on the measurement accuracy of a 10 mL syringe, the volume per nebulizer has been rounded to the nearest 0.2 mL. The total nebulization volume is based on the rounded volume per nebulizer and the number of nebulizers.

[c] Approximate nebulization time is based on a flow rate of 0.3 mL/minute for the InnoSpire Go nebulizer. This represents actual nebulization time and does not include the rest periods between nebulizer changes.

[d] The medication cup of the InnoSpire Go nebulizer holds a maximum of 8 mL of solution. As nebulizers will not be refilled during nebulization, multiple nebulizers, as shown in the table, will be used to deliver the specified volume for each of the dose levels of MRT5005. The MRT5005 suspension will be divided equally among the nebulizers.

Storage of Investigational Product:

MRT5005 vials should be stored frozen at -80°C ± 5°C (-112°F ± 9°F) in an appropriate freezer until the day of use.

Normal saline solution (placebo comparator) should be stored at controlled room temperature from 15°C to 30°C (59°F to 86°F).

Methodology:

General Study Design

At least 40 adult male and female patients with CF, 18 years of age or older, are planned to participate in the study. Patients who are clinically stable with a forced expiratory volume in 1 second (FEV_1) ≥50% and ≤90% predicted, and who meet all inclusion criteria and none of the exclusion criteria will be eligible for the study. Women of childbearing potential will also be eligible to participate if they are willing and able to comply with contraception requirements. Subjects will be enrolled at multiple centers in the US.

This Phase 1/2 study is designed as a randomized, double-blind, placebo-controlled, combined single and multiple ascending dose (SAD and MAD) trial, which will be conducted in 3 parts. Subjects will be administered single and multiple escalating doses of MRT5005 in Parts A and B of the study, respectively. In Part D, subjects will be administered 5 consecutive daily doses of 4 mg MRT5005 or placebo. There will be an option to enroll and treat additional groups, with up to a maximum of 44 evaluable subjects participating in the study. Subjects will not be allowed to participate in more than one part of the study.

Flow diagrams of subject enrollment and treatment allocation for Parts A, B, and D of the study are presented in Appendix 1.

In Part A of the study, 4 groups consisting of 4 subjects each will be enrolled sequentially to receive single doses of MRT5005 or placebo (normal saline) administered by nebulization. Four dose levels of MRT5005 will be investigated: 8, 16, 24, and 20 mg of [redacted] mRNA (the active drug substance of MRT5005). Within each dose group, the enrollment and treatment of the 4 subjects will be staggered by at least 1 week. Subjects will be randomized in a 3:1 ratio to receive a single dose of either MRT5005 or placebo (3 subjects to receive MRT5005 and 1 subject to receive placebo per dose group).

The Protocol Safety Review Committee (PSRC) will review blinded safety data to determine if escalation to the next higher dose level can proceed, as explained in Section 3.2.2.

The decision to begin enrollment and treatment of the initial 8 mg multiple-dose group in Part B will also be made by the PSRC, based on a review of at least 28 days of safety follow-up for all subjects who received a single dose of the 8 mg dose level in Part A.

In Part B, 4 groups consisting of 4 subjects each will receive multiple doses of nebulized MRT5005 or placebo administered by nebulization. Three groups will be enrolled sequentially to receive dose levels of MRT5005 investigated as single doses in Part A (8 mg, 16 mg, and 20 mg). An additional dose level that was not investigated in Part A (12 mg) will also be evaluated in Part B. The 12 mg dose group may

be enrolled in parallel with the 16 and/or 20 mg dose group. Within each dose group, subjects will be randomized in a 3:1 ratio to receive 5 doses of either MRT5005 or placebo (3 subjects to receive MRT5005 and 1 subject to receive placebo per dose group), administered 1 dose per week for 5 weeks. The enrollment and treatment of the 4 subjects within each dose group will be staggered by at least 2 weeks (the next subject in the dose group will only be enrolled and treated when the previous subject has received their second dose and there is approximately 1 week of safety follow-up), with the exception of the 12 mg dose group in Part B which will not require staggered treatment under the circumstances described in Section 3.1.

Escalation from 8 mg dose group to the 16 and 12 mg dose groups, and from 16 mg to the 20 mg dose group in Part B will occur after review of the following safety data by the PSRC:

1. At least 1 week of safety follow-up after the 3rd dose of the 4th (last) subject of the previous (lower) dose.
2. At least 28 days of safety follow-up after the dose of the 4th (last) subject of the corresponding single dose cohort. For instance, for the decision to escalate from the 8 mg to the 16 mg multiple dose cohort, the PSRC will review at least 7 days of safety follow-up after the 3rd dose of the 4th (last) subject receiving multiple doses of 8 mg, as well as at least 28 days of safety follow-up after the single dose of the 4th (last) subject receiving a single dose of 16 mg. Note that there is no corresponding single dose cohort for the 12 mg multiple dose group and therefore this requirement is not applicable.

In Part D, 8 subjects will be randomized in a 3:1 ratio to receive 5 doses of either 4 mg MRT5005 or placebo, administered at 1 dose per day for 5 consecutive days. Because single doses up to 20 mg, as well as 5 weekly doses up to 16 mg have been tolerated in Parts A and B, the enrollment and treatment of the 8 subjects within Part D will not be staggered. During the treatment of subjects in Part D, should AEs occur that indicate the study drug is not tolerated well, the enrollment and treatment of subjects may be terminated by the PSRC and Sponsor, and enrollment and treatment of a lower dose strength may be considered in the remaining subjects in the cohort. For example, if the tolerability of the 4 mg daily dose level is found to be unacceptable, then the 2 mg dose level can be considered for investigation.

The treatment randomization for the 8 mg, 16 mg, and 24 mg single dose groups will be unblinded 1 month after the last dose of the last subject in the 24 mg single dose group in Part A. The blind will be maintained in the 20 mg single dose group in Part A, as well as the 8, 16, and 12 mg multiple dose groups in Part B until the 1-month timepoint after the last dose (Day 57) of the last subject dosed in the 12 mg dose group. For the 20 mg multiple dose group in Part B (if applicable), the blind will be maintained until the last subject in this group has reached the 1-month timepoint after the last dose day (Day 57). For Part D, the blind will be maintained until the 1-month timepoint after the last dose (Day 32) of the last subject in Part D.

All subjects in the study will be monitored for safety for 12 months after administration of the last dose of investigational product (IP; post-single dose in Part A; post-fifth dose in Parts B and D). The safety and tolerability of nebulized MRT5005 will be assessed based on the types, frequency, and severity of treatment-emergent adverse events (AEs) reported including the number of pulmonary exacerbations; concomitant medication use; and changes from baseline in physical examination, weight, vital signs, oxygen saturation (pulse oximetry), electrocardiogram (ECG), standard clinical laboratory tests, chest x-ray, and spirometry as a measure of pulmonary function. As part of the safety evaluation, assays to detect [redacted] mRNA and [redacted] in the blood post-treatment will be performed along with assays to detect

antibody and T cell immune responses to CFTR protein and anti-PEG antibodies.

To maintain the study blind, the Investigators and all study staff involved in the evaluation of subject eligibility, administration of IP, and assessment of study outcomes will be blinded to treatment assignment (MRT5005 vs. placebo within each dose group) until planned unblinding. All subjects and their families, as well as Sponsor personnel in direct contact with the study center, will also be blinded. As the MRT5005 suspension and normal saline placebo will appear different, designated unblinded members of the study staff and/or pharmacy will be responsible for preparing and dispensing the IP into the nebulizers, as well as for randomizing subjects. The unblinded individuals will not participate in any other part of the study.

Schedule of Procedures for Screening, Treatment, and Follow-up Periods

Each part of the study will consist of 3 periods: a screening period, a treatment period, and a follow-up period. The procedures and tests to be performed during each of these periods in Parts A, B, and D of the study are presented in Table 1 through Table 9.

Part A: Screening Period (Day -28 to Day -2, Table 1)

During the screening period (from Day -28 to Day -2), informed consent will be obtained from the subject; inclusion and exclusion criteria will be reviewed; and subject eligibility for the study will be determined based on the procedures and tests performed during this period. Collection of AEs and serious adverse events (SAEs), regardless of relationship, and concomitant medications will begin from the time the subject signs the informed consent.

Part A: Treatment Period (Day -1 to Day 2, Table 1)

During the treatment period, subjects participating in Part A will be confined to the study center (inpatient) from Day -1 to Day 2. On Day -1, eligible subjects will perform the baseline procedures and tests. On Day 1, the pre-dose assessments should be performed immediately prior to IP administration. The procedures and tests performed on Day -1 and pre-dose on Day 1 will be used to confirm eligibility.

Prior to IP administration on Day 1, subjects should undergo their routine pulmonary therapies (airway clearance and pulmonary medications). If a subject is receiving inhaled rhDNase (PULMOZYME), this treatment should be withheld 24 hours before and after dosing with IP. The administration of IP should optimally occur within 2 to 3 hours after subjects have completed their pulmonary therapies for the day. Following randomization, IP will be administered by the respiratory route using an InnoSpire Go nebulizer.

Following IP administration, the Day 1 and 2 post-treatment procedures and tests will be performed at the protocol-specified time points. Subjects can be discharged when all of the Day 2 assessments have been completed and when subjects have been deemed clinically stable by the Investigator with no ongoing AEs or safety concerns. Subjects will be housed overnight close to the study center until the clinic visit on the following day (Day 3).

Part A: Follow-up Period (Day 3 to Day 337, Table 2 and Table 3)

Safety will be monitored for 12 months after administration of IP. Subjects will return for outpatient clinic visits on Days 3, 8, 15, 29, 57, 85, 169, 253, and 337 to perform the follow-up procedures and tests scheduled for this period. Telephone contact with the subject will occur on Days 5, 11, 18, 22, 43, 71, 113, 141, 197, 225, 281, and 309 to query the subject about the occurrence of any AEs/SAEs and any changes in concomitant medications.

Part B: Screening Period (Day -28 to Day -2, (Table 4)

The subjects participating in Part B of the study will perform the same procedures and tests during the

screening period as in Part A.

Part B: Treatment Period (Day -1 to Day 33, Table 4 and Table 7)

No confinement will be required of subjects in Part B; subjects will perform all clinic visits in the treatment period as outpatients.

On Day -1, eligible subjects will perform the baseline procedures and tests. On days in which IP is administered (Days 1, 8, 15, 22, and 29), the pre-dose assessments should be performed immediately prior to IP administration. The procedures and tests performed on Day -1 and Day 1 will be used to confirm eligibility. As described for Part A, prior to the administration of IP, subjects should undergo their routine pulmonary therapies (airway clearance and pulmonary medications). The administration of IP should optimally occur within 2 to 3 hours after subjects have completed their pulmonary therapies for the day. Following randomization, IP will be administered by the respiratory route using an InnoSpire Go nebulizer.

On dosing days, subjects will remain in the clinic for safety monitoring for at least 6 hours after administration of IP and will be discharged only when deemed clinically stable by the Investigator with no ongoing AEs or safety concerns of clinical significance. Discharged subjects can go home if they live locally (within 1 hour driving distance from the study center) or if not should be housed overnight close to the study center until the clinic visit on the following day (Days 2, 9, 16, 23, and 30). The subject will be contacted by telephone approximately 3 days after the clinic visit (Days 5, 12, 19, 26, and 33), to query the subject about the occurrence of any AEs/SAEs and any changes in concomitant medications.

Subjects will be provided a digital thermometer and Body Temperature Recording Log for measuring and recording body temperature on dosing days after discharge, at regular intervals until bedtime, and as needed overnight should febrile symptoms awaken the subject.

Part B: Follow-up Period (Day 36 to Day 365, Table 5 and Table 6)

Safety will be monitored for 12 months after administration of the fifth dose of IP. Subjects will return for outpatient clinic visits on Days 36, 43, 57, 71, 85, 113, 197, 281, and 365 to perform the follow-up procedures and tests scheduled for this period. Telephone contact with the subject will occur on Days 39, 46, 50, 64, 78, 99, 141, 169, 225, 253, 309, and 337 to query the subject about the occurrence of any AEs/SAEs and any changes in concomitant medications.

Part D: Screening Period (Day -28 to Day -1, Table 8)

Subjects participating in Part D of the study will perform the same procedures and tests during the screening period as in Parts A and B.

Part D: Treatment Period (Day 1 to Day 5, Table 8)

No confinement will be required of subjects in Part D; subjects will perform all clinic visits in the treatment period as outpatients. Pre-dose assessments on Day 1 should be performed prior to IP administration.

Prior to IP administration, subjects should undergo their routine pulmonary therapies (airway clearance and pulmonary medications). The administration of IP should optimally occur within 2 to 3 hours after subjects have completed their pulmonary therapies for the day. Following randomization, IP will be administered by the respiratory route using an InnoSpire Go nebulizer.

On each dosing day, subjects will remain in the clinic for safety monitoring for at least 2 hours after administration of IP and will be discharged only when deemed clinically stable by the Investigator with no ongoing AEs or safety concerns of clinical significance. Discharged subjects may go home if they live locally (within 1 hour driving distance from the study center) or if not should be housed overnight close to

the study center until the clinic visit on the following day. If a subject is experiencing an ongoing AE or there is a safety concern at the 2-hour time point (eg, decreased oxygen saturation by pulse oximetry or airway symptoms), based on the judgment of the Investigator, the subject should remain in the study center or hospital until the AE or safety concern has resolved and the subject is sufficiently stable to be discharged.

Subjects will be provided a digital thermometer and Body Temperature Recording Log for measuring and recording body temperature on dosing days after discharge, at regular intervals until bedtime, and as needed overnight should febrile symptoms awaken the subject.

Part D: Follow-up Period (Day 8 to Day 341, Table 8 and Table 9)

Safety will be monitored for approximately 12 months after administration of the fifth dose of IP. Subjects will return for outpatient clinic visits on Days 11, 18, 32, 60, 145, 229, and 341 to perform the follow-up procedures and tests scheduled for this period. Telephone contact with the subject will occur on Days 8, 25, 46, 89, 117, 173, 201, 257, 285, and 313 to query the subject about the occurrence of any AEs/SAEs and any changes in concomitant medications.

Inclusion and Exclusion Criteria:

To be considered for inclusion in this study, patients must meet all of the following inclusion and none of the exclusion criteria.

Inclusion Criteria:

1. Male and female patients with CF, 18 years of age or older
2. Confirmed diagnosis of CF as defined by both of the following:
    - Two CF disease-causing CFTR mutations in Class I or II (genotype confirmed at the screening visit). CFTR genotyping will only be performed if adequate prior documentation is not available.
    - Chronic sinopulmonary disease and/or gastrointestinal/nutritional abnormalities consistent with CF disease.
3. Clinically stable CF disease, as judged by the Investigator
4. FEV_1 ≥50% and ≤90% of the predicted normal for age, gender, and height at screening
5. Resting oxygen saturation ≥92% on room air (pulse oximetry)
6. Body mass index ≥17.5 kg/m^2 and weight ≥40 kg at screening
7. Willing to remain on stable CF medications for the duration of the study
    - Patients who are receiving lumacaftor/ivacaftor or tezacaftor/ivacaftor combination drugs (ORKAMBI or SYMDEKO) are eligible for the study; however, patients must have been on stable treatment with this medication for at least 28 days prior to the screening visit, and should remain on it for the duration of the study preferably at a stable dose.
8. Non-smoking for a minimum of 2 years
9. Willing and able to give written, signed, and dated informed consent to participate in the study
10. Willing and able to comply with scheduled visits, treatment, laboratory tests, restrictions, contraception requirements (Section 4.4), and other study procedures
    - Patients must have adequate clinical condition to safely undergo the planned study procedures
    - Willing and able to receive nebulized IP through a mouthpiece for up to 133 minutes

Exclusion Criteria:

1. History of any comorbidity that, in the opinion of the Investigator, could confound the results of the study, pose an additional risk from the IP or study procedures, could potentially contribute to the clinical instability of the subject during the study, or would make the subject unlikely to complete the study. This may include, but is not limited to a history of cardiovascular, renal, or central nervous system disease; history of serious mental illness; history or presence of clinically significant pathology including liver cirrhosis and/or portal hypertension; or history of uncontrolled CF-related diabetes.
2. An acute upper or lower respiratory infection, pulmonary exacerbation, or clinically significant episode of hemoptysis (>30 mL or in the opinion of the Investigator) within 28 days prior to Day 1.
3. Any of the following changes in medication prior to Day 1:
    - Any change in chronic respiratory medication within 28 days prior to Day 1.
    - Initiation of any new chronic therapy (eg, inhaled hypertonic saline, or inhaled antibiotic (tobramycin [TOBI], aztreonam [CAYSTON]) within 28 days prior to Day 1.
    - Use of antibiotics or oral steroids for acute symptoms within 14 days prior to Day 1.
4. Receiving treatment with ivacaftor monotherapy (KALYDECO).
5. Parts A and B only: Receiving treatment with triple combination therapy (TRIKAFTA). Patients with a prior history of treatment with TRIKAFTA are eligible to participate if treatment has been discontinued at least 28 days prior to Day 1.
6. Patients with a Class III, IV, or V CFTR gene mutation in at least 1 allele.
    - See Appendix 2 for guidance on the classification of CFTR mutations. As the phenotype and classification of some CFTR mutations remains uncertain, the eligibility of a patient with 1 of these mutations will be at the discretion of the Investigator and Sponsor, based on the patient's medical history.
7. Any of the following abnormal laboratory values at screening:
    - Hemoglobin <10 g/dL.
    - Serum albumin <2.5 g/dL.
    - Abnormal liver function defined as meeting any 3 or more of the following: ALT >3x upper limit of normal (ULN); AST >3x ULN; GGT >2.5x ULN; alkaline phosphatase >2.5x ULN; and total bilirubin >1.5x ULN (except for patients with isolated Gilbert Syndrome).
8. Any clinically significant abnormal laboratory test result prior to Day 1 that would interfere with the study assessments or indicate clinical instability of the patient, as judged by the Investigator.
9. Infection with highly virulent bacteria associated with accelerated decline in pulmonary function and/or decreased survival (eg, Burkholderia cenocepacia, Burkholderia dolosa, Mycobacterium abscessus). For a patient with a history of positive culture, he/she can be considered free of infection based on the following guidance:
    - All cultures obtained within the past 12 months should be negative for these bacteria. The patient should have had at least 2 cultures performed within the past 12 months, at least 3 months apart, with at least 1 culture obtained within 6 months of screening for this study.
10. History of or listed for solid organ or hematological transplantation.
11. Positive viral serology test results for HIV type 1 or 2 antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies at screening.
12. Positive test for drugs of abuse or alcohol at the screening visit.

13. Donation of blood or blood products within 60 days prior to the initial screening visit.
14. Participation in an investigational product or device study within 30 days prior to the initial screening visit or at any time during this Translate Bio-Sponsored study. (The 30-day window applies to investigational products with elimination half-lives of <6 days. If the elimination half-life of the investigational product is ≥6 days, then the window should be extended to at least 5 half-lives from the last dose administered.)
15. Prior enrollment in this study, with the exception of subjects who discontinued treatment after one dose of study drug for a reason unrelated to safety as specified in Section 7.1.1.2. (A patient is considered enrolled into the study when he or she has been randomized.)
16. Any suspicion of, or history of, alcohol and/or other substance abuse or addiction within the past year.
17. Pregnant or lactating females.
18. History of drug allergy or other allergy that, in the opinion of the Investigator, contraindicates participation (eg, history of allergy reactions that could interfere with the safety assessment of the IP).
19. History of allergic reactions to any component of the IP including its excipients.

Maximum duration of subject involvement in the study:

Planned maximum duration of study participation in Part A: up to 368 days. This consists of an initial screening period of up to 27 days, followed by 338 days [+3-day window] of the treatment and follow-up periods of the study.

Planned maximum duration of study participation in Part B: up to 396 days. This consists of an initial screening period of up to 27 days, followed by 366 days [+3 day window] of the treatment and follow-up periods of the study.

Planned maximum duration of study participation in Part D: up to 372 days. This consists of an initial screening period of up to 28 days, followed by 341 days (+ 3-day window) of the treatment and follow-up periods of the study.

Study Endpoints:

Primary endpoint

The safety and tolerability of nebulized MRT5005 will be assessed based on the types, frequency, and severity of treatment-emergent AEs including pulmonary exacerbations; concomitant medication use; and changes from baseline in physical examination, weight, vital signs, oxygen saturation (pulse oximetry), ECG, standard clinical laboratory tests, chest x-ray, and spirometry as a measure of pulmonary function.

Secondary endpoint

The biological activity of nebulized MRT5005 will be assessed based on changes from baseline in $ppFEV_1$ and other spirometry parameters.

Statistical analysis:

The sample size is not based on any statistical considerations. The sample size is based on traditional Phase 1/2, first-in-human study designs for this disease population.

All analyses will use descriptive rather than inferential approaches given the objectives of the study. This includes the primary endpoint analyses for safety as well as for the analyses of the secondary endpoints. All summaries will be displayed by treatment group. Summary statistics for continuous variables will include the number of subjects (N), mean, standard deviation, minimum, median, and maximum. For categorical data, summaries will include the frequency and percentage.

The primary analysis population for safety will be the safety analysis set, which will include all randomized subjects who received IP. Subject disposition, demographics and baseline characteristics, IP exposure, and prior and concomitant medications will be summarized. The number and percentage of treatment-emergent AEs will be calculated overall, by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized or listed. Results from vital sign and pulse oximetry measurements, clinical laboratory tests, ECGs, spirometry testing, and chest x-rays will be summarized by treatment, dose group, and visit. Clinically important findings will also be summarized or listed.

Table 1: Part A - Schedule of Procedures for the Screening and Treatment Periods - Day -28 to Day 2

	Screening Period	**Treatment Period**										
Study Week		**Baseline**	**Week 1**									
Study Day	**Day -28 to -2**	**Day -1**	**Day 1**									**Day 2**
Time point (Hours post nebulization)			**Pre-dose[a]**	**Dosing**	**0[b]** (±5 min)	**0.5** (±5 min)	**1** (±5 min)	**2** (±5 min)	**4** (±15 min)	**6** (±15 min)	**8[c]** (±15 min)	**24[d] (±2 hours)**
Screening Visit(s)[e]	X											
In-house confinement at study center (inpatient)		X	X	X	X	X	X	X	X	X	X	X
Informed consent (Part A)	X											
Inclusion/exclusion criteria	X	X										
Demography and medical/medication history	X	X										
Physical examination	X	X	X[f]		X[f]		X[f]	X[f]	X[f]		X[f]	X
Vital signs[g]												
• Blood pressure, pulse rate, body temperature	X	X	X	X[h]	X	X	X	X	X	X	X	X
• Respiratory rate	X	X	X		X	X	X	X	X	X	X	X
Pulse oximetry	X	X	X	X[i]	X	X	X	X	X	X	X	X
Height[j]	X											
Weight	X	X										
Electrocardiogram (ECG)	X	X	X[q]								X	X
Serum chemistry[s], hematology, coagulation, urinalysis, CRP	X	X										X
Serum or urine pregnancy test[k]	X	X										
Drug and alcohol screening	X											

Table 1: Part A - Schedule of Procedures for the Screening and Treatment Periods - Day -28 to Day 2

	Screening Period	Treatment Period									
Study Week		**Baseline**	**Week 1**								
Study Day	**Day -28 to -2**	**Day -1**	**Day 1**								**Day 2**
Time point (Hours post nebulization)			**Pre-dose[a]**	**Dosing**	**0[b]** (±5 min)	**0.5** (±5 min)	**1** (±5 min)	**2** (±5 min)	**4** (±15 min)	**6** (±15 min)	**8[c]** (±15 min)	**24[d]** **(±2 hours)**
Spirometry[l]	X	X	X[q]								X[l]	X
Viral screen (HIV, HBV, HCV)	X											
Chest x-ray[m]	X											
[redacted]mRNA and [redacted] assays[o]		X									X	X
Immune response assays[n,o]		X										
Adverse event collection[p]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication collection[p]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant surgical procedure collection[p]	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[q]			X									
IP dosing[r]				X								

Abbreviations: CRP: C reactive protein; HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; [redacted]

a The pre-dose assessments should be performed immediately prior to IP administration. If the subject is receiving treatment with a short-acting bronchodilator as part of their routine pulmonary therapies, pre-dose spirometry testing may be scheduled before the subject's pulmonary therapies (if the subject's schedule permits) so that it can be performed "pre-bronchodilator." See footnotes l and q.

b Hour 0 corresponds to the end of nebulization of IP.

c If there is ongoing AE or safety concern of clinical significance at the 8-hour time point (eg, decreased oxygen saturation or airway symptoms), appropriate monitoring should continue until the AE or safety concern has resolved.

d Subjects can be discharged when all of the Day 2 assessments have been completed and when subjects have been deemed clinically stable by the Investigator with no ongoing AEs or safety concerns of clinical significance. Discharged subjects should be housed overnight close to the study center until the clinic visit on the following day (Day 3). If a subject is experiencing an ongoing AE or there is a safety concern on Day 2, based on the judgment of the Investigator, the

subject can remain in the study center overnight or can be hospitalized for continued monitoring until the clinic visit on the following day (Day 3). The subject should remain in the study center or hospital until the AE or safety concern has resolved and the subject is sufficiently stable to be discharged.

e Multiple visits during the screening period may be necessary for the subject to complete all of the required screening procedures and tests.

f A limited physical examination will be performed at these time points.

g Blood pressure and pulse rate should be taken in a seated position after at least 5 minutes of rest.

h Blood pressure and pulse rate will be monitored continuously during nebulization of IP (except during rest periods), and will be recorded at the end of nebulization with each of the multiple nebulizers used to deliver the total volume of IP (eg, for the 16 mg dose, blood pressure and pulse rate will be recorded at the end of nebulization with each of the 4 nebulizers used to deliver the 28 mL total volume); the final recording will count as the Hour 0 time point. Blood pressure or pulse rate may be recorded more frequently, if clinically indicated. (Body temperature will not be monitored during the dosing period.)

i Oxygen saturation, measured by pulse oximetry, will be monitored continuously during nebulization of IP, and will be recorded at the end of nebulization with each of the multiple nebulizers used to deliver the total volume of IP (see footnote h for example); the final recording will count as the Hour 0 time point. Oxygen saturation may be recorded more frequently, if clinically indicated.

j All body mass index calculations will use the subject's height measured at the initial screening visit.

k A serum or urine β-hCG pregnancy test will be performed on all female subjects, regardless of childbearing potential, at the initial screening visit and on Day -l

l If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting bronchodilator (Section 7.5.2.12). The spirometry testing at the 8-hour time point on Day 1 has an expanded window of ±1 hour to accommodate this. If a subject experiences respiratory distress or pulmonary symptoms, at the discretion of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.

m Chest x-rays will consist of routine posterioranterior and lateral views. The baseline chest x-ray can be performed at any time from Day -14 to Day -2 during the screening period.

n Assays will measure antibody and T cell responses to CFTR protein as well as anti-PEG antibodies.

o In addition to the time points specified in the schedule of assessments, ad hoc testing for immune response assays and/or [redacted] mRNA and [redacted] assays may also be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events or unexplained bronchospasm.

p All AEs and SAEs, regardless of relationship, concomitant medications, and concomitant surgical procedures will be collected from the time the subject signs the inform consent.

q Subjects should be randomized following confirmation of eligibility on Day 1. Confirmation of eligibility on Day 1 requires a review of the Day -1 results and pre-dose Day 1 results of physical exam, AE, conmeds, vital signs and pulse oximetry. A subject is considered enrolled into the study when he or she has been randomized.

r The Day 1 pre-dose ECG and spirometry must be reviewed before the first dose may be administered. The administration of IP should optimally occur within 2-3 hours after subjects have completed their routine pulmonary therapies (airway clearance and pulmonary medications) for the day. For subjects whose pulmonary medications do not include an inhaled short-acting beta-agonist (or it is not given within the 2 to 3 hour window prior to IP administration),

albuterol (2 to 4 puffs) will be administered approximately 20 minutes before treatment with IP. IP will be administered by the respiratory route using an InnoSpire Go nebulizer. Depending on the dose level, nebulization times will range from approximately 44 to 133 minutes (represents actual nebulization times, and does not include the rest periods between nebulizer changes). During nebulization of IP, the subject should be monitored closely for any signs or symptoms of respiratory distress (eg, dyspnea, wheezing, bronchospasm)

s Subjects will be in a fasted state (8hrs without food or drink except water) for serum chemistry blood collections.

Table 2: Part A - Schedule of Procedures for the Follow-up Period - Day 3 to Day 85

	Follow-up Period											
Study Week	**Week 1 (cont'd)**		**Week 2[a]**		**Week 3[a]**		**Week 4**	**Week 5**	**Week 7**	**Week 9**	**Week 11**	**Week 13**
Study Day	**Day 3**	**Day 5**	**Day 8 (±1 day)**	**Day 11 (+3 or +4 days post Day 8)**	**Day 15 (±1 day)**	**Day 18 (+3 or +4 days post Day 15)**	**Day 22 (±2 days)**	**Day 29 (±2 days)**	**Day 43 (±3 days)**	**Day 57 (±3 days)**	**Day 71 (±3 days)**	**Day 85 (±3 days)**
Clinic visit (outpatient)[b]	X		X		X			X		X		X
Telephone contact		X		X		X	X		X		X	
Physical examination	X		X		X			X		X		X
Vital signs[c]												
• Blood pressure, pulse rate, body temperature	X		X		X			X		X		X
• Respiratory rate	X		X		X			X		X		X
Pulse oximetry	X		X		X			X		X		X
Weight			X		X			X		X		X
Electrocardiogram (ECG)			X		X			X		X		X
Serum chemistry[h], hematology, coagulation, urinalysis, CRP			X		X			X				X
Spirometry[d]	X		X		X			X		X		X
Chest x-ray[e]			X					X				
[redacted] mRNA and [redacted] assays[g]			X		X			X				
Immune response assays[f,g]					X			X				X
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X

Table 2: Part A - Schedule of Procedures for the Follow-up Period - Day 3 to Day 85

	Follow-up Period											
Study Week	**Week 1 (cont'd)**		**Week 2[a]**		**Week 3[a]**		**Week 4**	**Week 5**	**Week 7**	**Week 9**	**Week 11**	**Week 13**
Study Day	**Day 3**	**Day 5**	**Day 8 (±1 day)**	**Day 11 (+3 or +4 days post Day 8)**	**Day 15 (±1 day)**	**Day 18 (+3 or +4 days post Day 15)**	**Day 22 (±2 days)**	**Day 29 (±2 days)**	**Day 43 (±3 days)**	**Day 57 (±3 days)**	**Day 71 (±3 days)**	**Day 85 (±3 days)**
Concomitant medication collection	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant surgical procedure collection	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: CRP: C reactive protein; [redacted].

a The timing of the telephone contacts during Weeks 2 and 3 is based on the number of days (+3 or +4) after the actual visits for Days 8 and 15.

b Refer to Section 7.6 for onsite clinic visit flexibility due to coronavirus disease.

c Blood pressure and pulse rate should be taken in a seated position after at least 5 minutes of rest.

d If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting bronchodilator (Section 7.5.2.12). If a subject experiences respiratory distress or pulmonary symptoms, at the discretion of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.

e Chest x-rays will consist of routine posterioranterior and lateral views. At the discretion of the Investigator, an unscheduled chest x-ray may be performed at any time during the follow-up period if the subject is experiencing respiratory symptoms that warrant it.

f Assays will measure antibody and T cell responses to CFTR protein and anti-PEG antibodies.

g In addition to the time points specified in the schedule of assessments, ad hoc testing for immune response assays and/or [redacted] mRNA and [redacted] assays may also be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events or unexplained bronchospasm.

h Subjects will be in a fasted state (8hrs without food or drink except water) for serum chemistry study blood collections.

Table 3: Part A - Schedule of Procedures for the Follow-up Period - Day 113 to Day 337

	Follow-up Period								
Study Week	**Week 17**	**Week 21**	**Week 25**	**Week 29**	**Week 33**	**Week 37**	**Week 41**	**Week 45**	**Week 49**
Study Day	**Day 113 (±3 days)**	**Day 141 (±3 days)**	**Day 169 (±3 days)**	**Day 197 (±3 days)**	**Day 225 (±3 days)**	**Day 253 (±3 days)**	**Day 281 (±3 days)**	**Day 309 (±3 days)**	**Day 337 (±3 days)**
Clinic visit (outpatient)[a]			X			X			X
Telephone contact	X	X		X	X		X	X	
Physical examination			X			X			X
Vital signs[b]									
• Blood pressure, pulse, body temperature			X			X			X
• Respiratory rate			X			X			X
Pulse oximetry			X			X			X
Weight			X			X			X
Electrocardiogram (ECG)			X			X			X
Serum chemistry[f], hematology, coagulation, urinalysis, CRP			X						X
Spirometry[c]			X			X			X
Immune response assays[d]			X						X[c]
Serum or urine pregnancy test[e]									X
Adverse event collection	X	X	X	X	X	X	X	X	X
Concomitant medication collection	X	X	X	X	X	X	X	X	X
Concomitant surgical procedure collection	X	X	X	X	X	X	X	X	X

Abbreviations: CRP: C reactive protein.
a Refer to Section 7.6 for onsite clinic visit flexibility due to coronavirus disease.

b Blood pressure and pulse rate should be taken in a seated position after at least 5 minutes of rest.

c If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting bronchodilator (Section 7.5.2.12). If a subject experiences respiratory distress or pulmonary symptoms, at the discretion of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.

d Assays will measure antibody and T cell responses to CFTR protein and anti-PEG antibodies. The blood collections for any of these assays on the final study day (Day 337) are optional and will be driven by the observation of a de novo positive immune response after treatment (see Section 7.5.2.15). In the event of inconclusive, invalid, or missing assay results at the Day 169 visit, the blood collection for one or more of these assays will be taken at Day 337 at the discretion of the Sponsor. In addition to the time points specified in the schedule of assessments, ad hoc testing for immune response assays and/or [redacted]mRNA and[redacted] assays may also be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events or unexplained bronchospasm.

e A serum or urine β-hCG pregnancy test will be performed on all female subjects, regardless of childbearing potential, at the end of the study on Day 337. In addition, a serum or urine β-hCG pregnancy test should be performed on female subjects at any time pregnancy is suspected or upon withdrawal from the study (the latter applies to all female subjects, regardless of childbearing potential).

f Subjects will be in a fasted state (8hrs without food or drink except water) for serum chemistry blood collections.

Table 4: Part B - Schedule of Procedures for the Screening and Treatment Periods - Day -28 to Day 33

	Screening Period	Treatment Period																
Study Week		**Base-line**	**Week 1[a]**			**Week 2**			**Week 3**			**Week 4**			**Week 5**			
Study Day	**Day -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 5** +4 days post Dose 1 (±1 day)	**Day 8** (±1 day)	**Day 9** +1 day post Dose 2	**Day 12** +4 days post Dose 2 (±1 day)	**Day 15** (±1 day)	**Day 16** +1 day post Dose 3	**Day 19** +4 days post Dose 3 (±1 day)	**Day 22** (±1 day)	**Day 23** +1 day post Dose 4	**Day 26** +4 days post Dose 4 (±1 day)	**Day 29** (±1 day)	**Day 30** +1 day post Dose 5	**Day 33** +4 days post Dose 5 (±1 day)	
Investigational Product			**Dose 1**			**Dose 2**			**Dose 3**			**Dose 4**			**Dose 5**			
Screening Visit(s)[b]	X																	
Clinic visit - outpatient[c]		X	X[d]	X		X[d]	X		X[d]	X		X[d]	X		X[d]	X		
Telephone contact					X			X			X			X				X
Informed consent [e]	X																	
Inclusion/exclusion criteria	X	X																
Demography and medical/medication history	X																	
Physical examination	X	X	X[e]	X[f]		X[e]	X[f]		X[e]	X[f]		X[e]	X[f]		X[e]	X[f]		
Vital signs[g]																		
• Blood pressure, pulse, body temperature	X	X	X[h]	X		X[h]	X		X[h]	X		X[h]	X		X[h]	X		
• Respiratory rate	X	X	X[h]	X		X[h]	X		X[h]	X		X[h]	X		X[h]	X		
Pulse oximetry	X	X	X[i]	X		X[i]	X		X[i]	X		X[i]	X		X[i]	X		
Height[j]	X																	
Weight	X	X				X[k]			X[k]			X[k]			X[k]			
Serum chemistry[w], hematology, coagulation, urinalysis, CRP	X	X							X[l]						X[l]	X		

Table 4: Part B - Schedule of Procedures for the Screening and Treatment Periods - Day -28 to Day 33

	Screening Period	Treatment Period																
Study Week		**Base-line**	**Week 1[a]**			**Week 2**			**Week 3**			**Week 4**			**Week 5**			
Study Day	**Day -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 5** +4 days post Dose 1 (±1 day)	**Day 8** (±1 day)	**Day 9** +1 day post Dose 2	**Day 12** +4 days post Dose 2 (±1 day)	**Day 15** (±1 day)	**Day 16** +1 day post Dose 3	**Day 19** +4 days post Dose 3 (±1 day)	**Day 22** (±1 day)	**Day 23** +1 day post Dose 4	**Day 26** +4 days post Dose 4 (±1 day)	**Day 29** (±1 day)	**Day 30** +1 day post Dose 5	**Day 33** +4 days post Dose 5 (±1 day)	
Investigational Product			**Dose 1**			**Dose 2**			**Dose 3**			**Dose 4**			**Dose 5**			
Serum or urine pregnancy test[m]	X	X																
Drug and alcohol screening	X																	
Spirometry	X	X	X[n]	X		X[n]	X		X[n]	X		X[n]	X		X[n]	X		
Viral screening (HIV, HBV, HCV)	X																	
Chest x-ray[o]	X																	
Electrocardiogram (ECG)	X	X		X					X[p]						X[p]	X		
[redacted] mRNA and [redacted] assays[s]		X		X		X[q]									X[q]	X		
Immune response assays[r,s]		X																
CFQ-R		X																
Adverse event collection[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication collection[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant surgical procedure collection[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization[u]			X															
IP dosing[v]			X			X			X			X			X			
Dispense thermometer			X															

Table 4: Part B - Schedule of Procedures for the Screening and Treatment Periods - Day -28 to Day 33

	Screening Period	Treatment Period																
Study Week		**Base-line**	**Week 1[a]**			**Week 2**			**Week 3**			**Week 4**			**Week 5**		
Study Day	**Day -28 to -2**	**Day -1**	**Day 1**	**Day 2**	**Day 5** +4 days post Dose 1 (±1 day)	**Day 8** (±1 day)	**Day 9** +1 day post Dose 2	**Day 12** +4 days post Dose 2 (±1 day)	**Day 15** (±1 day)	**Day 16** +1 day post Dose 3	**Day 19** +4 days post Dose 3 (±1 day)	**Day 22** (±1 day)	**Day 23** +1 day post Dose 4	**Day 26** +4 days post Dose 4 (±1 day)	**Day 29** (±1 day)	**Day 30** +1 day post Dose 5	**Day 33** +4 days post Dose 5 (±1 day)
Investigational Product			**Dose 1**			**Dose 2**			**Dose 3**			**Dose 4**			**Dose 5**		
Distribute Body Temp Log			X			X			X			X			X		
Collect Body Temp Log				X			X			X			X			X	
20 mg Dose Group Only																	
Serum inflammatory markers[s]		X		X		X[q]									X[q,]	X	

Abbreviations: CRP: C reactive protein; HIV: human immunodeficiency virus; HBV: hepatitis B virus; HCV: hepatitis C virus; [redacted] CFQ-R: Cystic Fibrosis Questionnaire-Revised.

a IP dosing should occur on approximately the same day of Weeks 1 through 5 (eg, every Tuesday [the day of the week is defined by the first dose given on Day 1 of Week 1]), but may occur ±1 day of the target day for Weeks 2 through 5 in order to facilitate subject scheduling. If at all possible, missed dosing of IP should be avoided. As such, if a subject is outside of the recommended window, the subject can be administered IP up to 3 days after the target day (eg, if the target day is Tuesday, then IP can be administered up to Friday). The subsequent dosing of IP can return to the original schedule. Except for Day 2 of Week 1, the timing of the clinic visits and telephone contacts post-treatment during Weeks 1 through 5 is based on the number of days after actual dosing of IP during that week.

b Multiple visits during the screening period may be necessary for the subject to complete all of the required screening procedures and tests.

c Subjects will perform all clinic visits in Part B of the study as outpatients.

d See Table 7 for the schedule of procedures and tests, and instructions on safety monitoring and discharge of subjects on the day of dosing. Discharged subjects can go home if they live locally (within 1 hour driving distance from the study center) or if not should be housed overnight close to the study center until the clinic visit on the following day.

e See Table 7 for the schedule and details of the physical examinations to be performed on the day of dosing.

f A limited physical examination will be performed at these time points.

g Blood pressure and pulse rate should be taken in a seated position after at least 5 minutes of rest.

h See Table 7 for the schedule of vital sign measurements to be performed on the dosing days.

i See Table 7 for the schedule of pulse oximetry measurements to be performed on the dosing days.

j All body mass index calculations will use the subject's height measured at the initial screening visit.

k Weight will be measured as a pre-dose assessment on dosing Days 8, 15, 22, and 29 (Table 7).

l Serum chemistry, hematology, coagulation, urinalysis, and CRP will be measured as pre-dose assessments on dosing Days 15 and 29 (Table 7).

m A serum or urine β-hCG pregnancy test will be performed on all female subjects, regardless of childbearing potential, at the initial screening visit and on Day -1.

n Spirometry will be performed pre-dose and at the 6-hour post-treatment time point on all dosing days (Table 7). If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting bronchodilator (Section 7.5.2.12). If a subject experiences respiratory distress or pulmonary symptoms, at the discretion of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.

o Chest x-rays will consist of routine posterioranterior and lateral views. The baseline chest x-ray can be performed at any time from Day -14 to Day -2 during the screening period. In addition, at the discretion of the Investigator, an unscheduled chest x-ray may be performed at any time during the treatment period if the subject is experiencing respiratory symptoms that warrant it.

p An electrocardiogram will be performed pre-dose on dosing Day 15; and pre-dose and 6 hours after treatment on dosing Day 29 (Table 7).

q Inflammatory markers (20 mg dose group only), as well as [redacted] mRNA and [redacted] will be measured as pre-dose assessments on dosing Days 8 and 29 (Table 7).

r Assays will measure antibody and T cell responses to CFTR protein and anti-PEG antibodies.

s In addition to the time points specified in the schedule of assessments, ad hoc testing for immune response assays, inflammatory markers (20 mg dose group only), and/or [redacted] mRNA and [redacted] assays may also be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events or unexplained bronchospasm.

t All AEs and SAEs, regardless of relationship, concomitant medications, and concomitant surgical procedures will be collected from the time the subject signs the informed consent form.

u See Table 7 for instructions on randomization of subjects on Day 1.

v See Table 7 for details on dosing of IP.

w Subjects will be in a fasted state (8hrs without food or drink except water) for serum chemistry study blood collections.

Table 5: Part B - Schedule of Procedures for the Follow-up Period - Day 36 to Day 113

	Follow-up Period											
Study Week	**Week 6[a]**		**Week 7[a]**		**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**	**Week 13**	**Week 15**	**Week 17**
Study Day	**Day 36 (±1 day)**	**Day 39 (+3 or +4 days post Day 36)**	**Day 43 (±1 day)**	**Day 46 (+3 or +4 days post Day 43)**	**Day 50 (±2 days)**	**Day 57 (±2 days)**	**Day 64 (±3 days)**	**Day 71 (±3 days)**	**Day 78 (±3 days)**	**Day 85 (±3 days)**	**Day 99 (±3 days)**	**Day 113 (±3 days)**
Clinic visit - outpatient[b]	X		X			X		X		X		X
Telephone contact		X		X	X		X		X		X	
Physical examination	X		X			X		X		X		X
Vital signs[c]												
• Blood pressure, pulse, body temperature	X		X			X		X		X		X
• Respiratory rate	X		X			X		X		X		X
Pulse oximetry	X		X			X		X		X		X
Weight	X		X			X		X		X		X
Electrocardiogram (ECG)	X		X			X				X		X
Serum chemistry[h], hematology, coagulation, urinalysis, CRP	X		X			X						X
Serum inflammatory markers (20 mg dose group only)[g]	X											
Spirometry[d]	X		X			X		X		X		X
Chest x-ray[e]	X					X						
[redacted] mRNA and [redacted] assays[g]	X		X			X						
Immune response assays[f,g]	X					X						X

Table 5: Part B - Schedule of Procedures for the Follow-up Period - Day 36 to Day 113

	Follow-up Period											
Study Week	**Week 6[a]**		**Week 7[a]**		**Week 8**	**Week 9**	**Week 10**	**Week 11**	**Week 12**	**Week 13**	**Week 15**	**Week 17**
Study Day	**Day 36 (±1 day)**	**Day 39 (+3 or +4 days post Day 36)**	**Day 43 (±1 day)**	**Day 46 (+3 or +4 days post Day 43)**	**Day 50 (±2 days)**	**Day 57 (±2 days)**	**Day 64 (±3 days)**	**Day 71 (±3 days)**	**Day 78 (±3 days)**	**Day 85 (±3 days)**	**Day 99 (±3 days)**	**Day 113 (±3 days)**
CFQ-R	X		X			X				X		X
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication collection	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant surgical procedure collection	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: CRP: C reactive protein; [redacted]; CFQ-R: Cystic Fibrosis Questionnaire-Revised.

a The timing of the telephone contacts during Weeks 6 and 7 is based on the number of days (+3 or +4) after the actual visits for Days 36 and 43.

b Refer to Section 7.6 for onsite clinic visit flexibility due to coronavirus disease.

c Blood pressure and pulse rate should be taken in a seated position after at least 5 minutes of rest.

d If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting bronchodilator (Section 7.5.2.12). If a subject experiences respiratory distress or pulmonary symptoms, at the discretion of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.

e Chest x-rays will consist of routine posterioranterior and lateral views. At the discretion of the Investigator, an unscheduled chest x-ray may be performed at any time during the follow-up period if the subject is experiencing respiratory symptoms that warrant it.

f Assays will measure antibodies and T cell responses to CFTR protein and anti-PEG antibodies.

g In addition to the time points specified in the schedule of assessments, ad hoc testing for immune response assays, inflammatory markers (20 mg dose group only), and/or [redacted] mRNA and[redacted] assays may also be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events or unexplained bronchospasm.

h Subjects will be in a fasted state (8hrs without food or drink except water) for serum chemistry study blood collections.

Table 6: Part B - Schedule of Procedures for the Follow-up Period - Day 141 to Day 365

	Follow-up Period								
Study Week	**Week 21**	**Week 25**	**Week 29**	**Week 33**	**Week 37**	**Week 41**	**Week 45**	**Week 49**	**Week 53**
Study Day	**Day 141 (±3 days)**	**Day 169 (±3 days)**	**Day 197 (±3 days)**	**Day 225 (±3 days)**	**Day 253 (±3 days)**	**Day 281 (±3 days)**	**Day 309 (±3 days)**	**Day 337 (±3 days)**	**Day 365 (±3 days)**
Clinic visit (outpatient)[a]			X			X			X
Telephone contact	X	X		X	X		X	X	
Physical examination			X			X			X
Vital signs[b]									
• Blood pressure, pulse, body temperature			X			X			X
• Respiratory rate			X			X			X
Pulse oximetry			X			X			X
Weight			X			X			X
Electrocardiogram (ECG)			X			X			X
Serum chemistry[f], hematology, coagulation, urinalysis, CRP			X						X
Spirometry[c]			X			X			X
Immune response assays[d]			X						X[c]
Serum or urine pregnancy test[e]									X
CFQ-R			X			X			X
Adverse event collection	X	X	X	X	X	X	X	X	X
Concomitant medication collection	X	X	X	X	X	X	X	X	X
Concomitant surgical procedure collection	X	X	X	X	X	X	X	X	X

Abbreviations: CRP: C reactive protein; CFQ-R: Cystic Fibrosis Questionnaire-Revised.

a Refer to Section 7.6 for onsite clinic visit flexibility due to coronavirus disease.

b Blood pressure and pulse rate should be taken in a seated position after at least 5 minutes of rest.

c If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting bronchodilator (Section 7.5.2.12). If a subject experiences respiratory distress or pulmonary symptoms, at the discretion of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.

d Assays will measure antibody and T cell responses to CFTR protein and anti-PEG antibodies. The blood collections for any of these assays on the final study day (Day 365) are optional and will be driven by the observation of a de novo positive immune response after treatment (Section 7.5.2.15). In the event of inconclusive, invalid, or missing assay results at the Day 197 visit, the blood collection for one or more of these assays will be taken at Day 365 at the discretion of the Sponsor. In addition to the time points specified in the schedule of assessments, ad hoc testing for immune response assays, inflammatory markers (20 mg dose group only), and/or [redacted] mRNA and [redacted] assays may also be performed when immunogenicity is suspected, such as allergy/hypersensitivity events or unexplained bronchospasm.

e A serum or urine β-hCG pregnancy test will be performed on all female subjects, regardless of childbearing potential, at the end of the study on Day 365. In addition, a serum or urine β-hCG pregnancy test should be performed on female subjects at any time pregnancy is suspected or upon withdrawal from the study (the latter applies to all female subjects, regardless of childbearing potential).

f Subjects will be in a fasted state (8hrs without food or drink except water) for serum chemistry study blood collections.

Table 7: Part B - Schedule of Procedures for Dosing Days - Weeks 1 Through 5

Study Day	**Dosing Days 1, 8, 15, 22, and 29**							
Time point (Hours post nebulization)	**Pre-dose[a]**	**Dosing**	**0[b]** (±5 min)	**0.5** (±5 min)	**1** (±5 min)	**2** (±5 min)	**4** (±15 min)	**6[c]** (±15 min)
Physical examination	X[d]		X[e]		X[e]	X[e]	X[e]	X[e]
Vital signs[f]								
• Blood pressure, pulse, body temperature	X	X[g]	X	X	X	X	X	X
• Respiratory rate	X		X	X	X	X	X	X
Pulse oximetry	X	X[h]	X	X	X	X	X	X
Spirometry[i]	X							X[i]
Adverse event collection	X	X	X	X	X	X	X	X
Concomitant medication collection	X	X	X	X	X	X	X	X
Concomitant surgical procedure collection	X	X	X	X	X	X	X	X
IP dosing[j]		X						
	Dosing Day 1 only							
Randomization[k]	X							
	Dosing Days 15 and 29 only							
Serum chemistry[m], hematology, coagulation, urinalysis, CRP	X							
Electrocardiogram (ECG)	X[l]							X[l]
	Dosing Days 8 and 29 only							
[redacted]mRNA and[redacted] assays	X							
Serum inflammatory markers (20 mg dose group only)	X							
	Dosing Days 8, 15, 22 and 29 only							
Weight	X							

Abbreviations: CRP: C reactive protein; [redacted]

a The pre-dose assessments should be performed immediately prior to IP administration. If the subject is receiving treatment with a short-acting bronchodilator as part of their routine pulmonary therapies, pre-dose spirometry testing may be scheduled before the subject's pulmonary therapies (if the subject's schedule permits) so that it can be performed "pre-bronchodilator." (See footnotes i and k).

b Hour 0 corresponds to the end of nebulization of IP.

c Subjects will remain in the study center for safety monitoring for at least 6 hours after the administration of IP and will be discharged only when deemed clinically stable by the Investigator with no ongoing AEs or safety concerns of clinical significance. Discharged subjects can go home if they live locally (within 1 hour driving distance from the study center) or if not should be housed overnight close to the study center until the clinic visit on the following day. If a subject is experiencing an ongoing AE or there is a safety concern (eg, decreased oxygen saturation or airway symptoms), based on the judgment of the Investigator, the subject can remain in the study center overnight or can be hospitalized for continued monitoring until the clinic visit on the following day. The subject should remain in the study center or hospital until the AE or safety concern has resolved and the subject is sufficiently stable to be discharged.

d The pre-dose physical examination on Day 1 will be a limited physical examination as a complete baseline physical examination will have already been performed the day before on Day -1. On all other dosing days (Days 8, 15, 22, and 29), a complete physical examination will be performed at the pre-dose time point.

e A limited physical examination will be performed at these time points.

f Blood pressure and pulse rate should be taken in a seated position after at least 5 minutes of rest.

g Blood pressure and pulse rate will be monitored continuously during nebulization of IP (except during rest periods), and will be recorded at the end of nebulization with each of the multiple nebulizers used to deliver the volume of IP (eg, for the 16 mg dose, blood pressure and pulse rate will be recorded at the end of nebulization with each of the 4 nebulizers used to deliver the 28 mL total volume); the final recording will count as the Hour 0 time point. Blood pressure or pulse rate may be recorded more frequently, if clinically indicated. (Body temperature will not be monitored during the dosing period).

h Oxygen saturation, measured by pulse oximetry, will be monitored continuously during nebulization of IP (except during rest periods), and will be recorded at the end of nebulization with each of the multiple nebulizers used to deliver the total volume of IP (see footnote g for example); the final recording will count as the Hour 0 time point. Oxygen saturation may be recorded more frequently, if clinically indicated.

i If feasible for the subject, spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting bronchodilator (Section 7.5.2.12). The spirometry testing at the 6-hour time point has an expanded window of ±1 hour to accommodate this.

j The Day 1 pre-dose ECG and spirometry must be reviewed prior to the first dose. The administration of IP should optimally occur within 2-3 hours after subjects have completed their routine pulmonary therapies (airway clearance and pulmonary medications) for the day. For subjects whose pulmonary medications do not include an inhaled short-acting beta-agonist (or it is not given within the 2-3 hour window prior to IP administration), albuterol (2 to 4 puffs) will be administered approximately 20 minutes before treatment with IP. IP will be administered by the respiratory route using an InnoSpire Go nebulizer. Depending on the dose level, nebulization times will range from approximately 44 to 133 minutes. During nebulization of IP, the subject should be monitored closely for any signs or symptoms of respiratory distress (eg, dyspnea, wheezing, bronchospasm).

k Subjects should be randomized following confirmation of eligibility on Day 1. Confirmation of eligibility on Day 1 requires a review of the Day -1 results and pre-dose Day 1 results of physical exam, AE, conmeds, vital signs and pulse oximetry. A subject is considered enrolled into the study when he or she has been randomized.

l An electrocardiogram will be performed pre-dose on dosing Day 15; and pre-dose and 6 hours after treatment on dosing Day 29.
m Subjects will be in a fasted state (8hrs without food or drink except water) for serum chemistry study blood collections.

Table 8: Part D - Schedule of Procedures for Screening through Day 18

	Screening Period	Treatment Period										Follow-Up Period		
Study Day	**Day -28 to -1**	**Day 1[a]**		**Day 2**		**Day 3**		**Day 4**		**Day 5**		**Day 8 (±1 day)**	**Day 11 (±1 day)**	**Day 18 (±1 day)**
		Pre-Dose	**2 hours post-dose**	**Pre-Dose**	**2 hours post-dose**	**Pre-Dose**	**2 hours post-dose**	**Pre-Dose**	**2 hours post-dose**	**Pre-Dose**	**2 hours post-dose**			
Clinic visit (outpatient)[a]	X	X	X	X	X	X	X	X	X	X	X		X	X
Telephone contact												X		
Informed consent	X													
Inclusion/exclusion criteria	X	X												
Demography and medical/medication history	X													
Full Physical examination	X												X	X
Limited physical exam		X	X	X	X	X	X	X	X	X	X			
Vital signs (BP, HR, body temperature, RR)[b]	X	X	X	X	X	X	X	X	X	X	X		X	X
Pulse oximetry	X	X	X	X	X	X	X	X	X	X	X		X	X
Height[c]	X													
Weight	X													
Serum chemistry, hematology, coagulation, urinalysis, CRP	X	X				X				X			X	X
Serum inflammatory markers[h]		X		X		X		X		X			X	X
Serum or urine pregnancy test[d]	X	X												
Drug and alcohol screening	X													
Spirometry[e]	X	X	X	X		X		X		X			X	X

Table 8: Part D - Schedule of Procedures for Screening through Day 18

	Screening Period	Treatment Period										Follow-Up Period		
Study Day	**Day -28 to -1**	**Day 1[a]**		**Day 2**		**Day 3**		**Day 4**		**Day 5**		**Day 8 (±1 day)**	**Day 11 (±1 day)**	**Day 18 (±1 day)**
		Pre-Dose	**2 hours post-dose**	**Pre-Dose**	**2 hours post-dose**	**Pre-Dose**	**2 hours post-dose**	**Pre-Dose**	**2 hours post-dose**	**Pre-Dose**	**2 hours post-dose**			
Viral screening (HIV, HBV, HCV)	X													
Chest x-ray[f]	X												X	
Electrocardiogram (ECG)	X										X			
[redacted]mRNA and [redacted] assays[h]		X	X	X	X	X	X	X	X	X	X		X	X
Immune response assays[g,h]		X											X	X
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant surgical procedure collection	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense thermometer & Body Temp Log			X											
Collect Body Temp Log				X		X		X		X			X	
Randomization[i]		X												

Abbreviations: BP: blood pressure; CRP: C reactive protein; HR: heart rate; [redacted] RR: respiratory rate

a Refer to Section 7.6 for onsite clinic visit flexibility due to coronavirus disease.

b Blood pressure and pulse rate should be taken in a seated position after at least 5 minutes of rest.

c All body mass index calculations will use the subject's height measured at the initial screening visit.

d A serum or urine β-hCG pregnancy test will be performed on all female subjects, regardless of childbearing potential, at the initial screening visit and on Day 1 (pre-dose)

e If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting bronchodilator (Section 7.5.2.12). If a subject experiences respiratory distress or pulmonary symptoms, at the discretion of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.

f Chest x-rays will consist of routine posterior, anterior and lateral views. At the discretion of the Investigator, an unscheduled chest x-ray may be performed at any time during the follow-up period if the subject is experiencing respiratory symptoms that warrant it.

g Assays will measure antibody and T cell responses to CFTR protein as well as anti-PEG antibodies.

h In addition to the time points specified in the schedule of assessments, ad hoc testing for immune response assays, inflammatory markers, and/or [redacted] mRNA and [redacted] may be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events or unexplained bronchospasm.

i Subjects should be randomized following confirmation of eligibility on Day 1. Confirmation of eligibility on Day 1 requires a review of the pre-dose Day 1 results of physical exam, AE, conmeds, vital signs, pulse oximetry, and pregnancy test (female subjects only). A subject is considered enrolled into the study when he or she has been randomized.

Table 9: Part D - Schedule of Procedures for the Follow-up Period - Day 25 to Day 341

	Follow-up Period											
Study Day	**Day 25 (±1 day)**	**Day 32 (±2 days)**	**Day 46 (±2 days)**	**Day 60 (±2 days)**	**Day 89 (±3 days)**	**Day 117 (±3 days)**	**Day 145 (±3 days)**	**Day 173 (±3 days)**	**Day 201 (±3 days)**	**Day 229 (±3 days)**	**Day 257, Day 285, Day 313 (±3 days)**	**Day 341 (±3 days)**
Clinic visit (outpatient)[a]		X		X			X			X		X
Telephone contact	X		X		X	X		X	X		X	
Physical examination		X		X			X			X		X
Vital signs (BP, HR, body temperature, RR)[b]		X		X			X			X		X
Pulse oximetry		X		X			X			X		X
Weight		X		X			X			X		X
Electrocardiogram (ECG)		X		X			X			X		X
Serum chemistry, hematology, coagulation, urinalysis, CRP		X		X			X			X		X
Serum Inflammatory markers[e]		X										
Spirometry[c]		X		X			X			X		X
Chest x-ray		X										
[redacted]mRNA and [redacted] assays[e]		X										
Immune response assays[d,e]		X					X			X		X
Serum or urine pregnancy test[f]												X
Adverse event collection	X	X	X	X	X	X	X	X	X	X	X	X

Table 9: Part D - Schedule of Procedures for the Follow-up Period - Day 25 to Day 341

	Follow-up Period											
Study Day	**Day 25 (±1 day)**	**Day 32 (±2 days)**	**Day 46 (±2 days)**	**Day 60 (±2 days)**	**Day 89 (±3 days)**	**Day 117 (±3 days)**	**Day 145 (±3 days)**	**Day 173 (±3 days)**	**Day 201 (±3 days)**	**Day 229 (±3 days)**	**Day 257, Day 285, Day 313 (±3 days)**	**Day 341 (±3 days)**
Concomitant medication collection	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant surgical procedure collection	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BP: blood pressure; CRP: C reactive protein; HR: heart rate; [redacted]RR: respiratory rate

a Refer to Section 7.6 for onsite clinic visit flexibility due to coronavirus disease.

b Blood pressure and pulse rate should be taken in a seated position after at least 5 minutes of rest.

c If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting bronchodilator (Section 7.5.2.12). If a subject experiences respiratory distress or pulmonary symptoms, at the discretion of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.

d Assays will measure antibody and T cell responses to CFTR protein and anti-PEG antibodies. The blood collections for any of these assays on the final study day (Day 341) are optional and will be driven by the observation of a de novo positive immune response after treatment (see Section 7.5.2.15). In the event of inconclusive, invalid, or missing assay results at the Day 145 visit, the blood collection for one or more of these assays will be taken at Day 341 at the discretion of the Sponsor.

e In addition to the time points specified in the schedule of assessments, ad hoc testing for immune response assays, inflammatory markers, and/or [redacted] mRNA and [redacted] may also be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events or unexplained bronchospasm.

f A serum or urine β-hCG pregnancy test will be performed on all female subjects, regardless of childbearing potential, at the end of the study on Day 341. In addition, a serum or urine β-hCG pregnancy test should be performed on female subjects at any time pregnancy is suspected or upon withdrawal from the study (the latter applies to all female subjects, regardless of childbearing potential).

1. BACKGROUND INFORMATION

1.1. Cystic fibrosis

Cystic fibrosis (CF), also known as mucoviscidosis, is an autosomal recessive genetic disorder that affects most critically the lungs, but also the pancreas, liver, and intestine.[1–3] It is characterized by abnormal transport of chloride and sodium across the epithelium, leading to thick, viscous secretions resulting from mutations in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR).[3,4] This protein functions as a channel that transports chloride ions across the membrane of cells and is required to regulate the components of mucus, sweat, saliva, tears, and digestive enzymes. Most CF patients develop severe, chronic lung disease related to airway obstruction partly due to increased levels of sulfated mucins, inflammation and recurrent bacterial infections that are eventually lethal; the median predicted survival age in the US of those born in 2017 is 46.2 years.[5] CF is the most frequent lethal genetic disease in the white population. There are approximately 30,000 individuals affected in the US, and 70,000 worldwide.[1,6–8] Incidence varies widely according to country and ethnicity. In the US, estimates of incidence range from 1 in 1,900-3,700 white Americans.[1,6] CF is present, but less frequent, in other US groups: estimated incidences in Hispanic, Asian, and Black American populations have been reported to be 1 in 9,200, 1 in 31,000, and 1 in 15,000, respectively.[9] There is wide country variability within Europe, ranging from 1 in 1,800 in Ireland to 1 in 25,000 in Finland.[10] CF is uncommon in Africa and Asia, with an incidence of 1 in 350,000 reported in Japan.[3]

Symptoms of CF often appear in infancy and childhood, the most frequent of which are respiratory symptoms, followed by failure to thrive, steatorrhea, and meconium ileus.[1] The lungs of individuals with CF are colonized and infected by bacteria from an early age. This leads to chronic airway infection and inflammation, progressing to bronchiectasis, gas trapping, hypoxemia, and hypercarbia. Pulmonary insufficiency is responsible for 70.5% of CF-related deaths in the US.[5] In the initial stage, common bacteria such as Staphylococcus aureus and Hemophilus influenzae colonize and infect the lungs. Eventually, Pseudomonas aeruginosa (and sometimes Burkholderia cepacia) dominates. By 18 years of age, 80% of patients with classic CF harbor P. aeruginosa, and 3.5% harbor B. cepacia. Once within the lungs, these bacteria adapt to the environment and develop resistance to commonly used antibiotics.

Non-pulmonary complications of CF result from blockages of affected organs with thickened mucosal secretions. These blockages cause damage in the pancreas, liver, and intestines leading to exocrine pancreatic insufficiency, malabsorption, and recurrent pancreatitis; CF-related diabetes; chronic hepatobiliary disease and cirrhosis; and meconium ileus and distal intestinal obstructive syndrome.[1,3] Male infertility due to azoospermia secondary to congenital absence of the vas deferens is also a common complication of CF.

The underlying defect causing CF is abnormal epithelial anion transport due to the lack of expression or dysfunction of the CFTR protein. The CFTR protein primarily functions as a chloride channel in epithelial cell membranes; however, it also involved in a number of other cellular membrane functions such as inhibition of sodium transport through the epithelial sodium channel, regulation of the outwardly rectifying chloride channel, and regulation of adenosine

triphosphate (ATP) channels.[3] CF is caused by mutations in the gene encoding for the CFTR protein, of which more than 2,000 mutations have been identified.[11] The more common gene mutations result in the lack of synthesis of the CFTR protein (class I), defective processing and maturation of the CFTR protein (class II), or the expression of a CFTR protein defective in regulation, eg, diminished ATP binding and hydrolysis (class III).[4] A deletion of phenylalanine at position 508 (F508del) is the most common CFTR mutation worldwide and is a class II defect in which the misfolded CFTR protein is rapidly degraded by the cell soon after synthesis.[4] The lack of a functional CFTR protein causes mucosal obstruction of exocrine glands in CF patients secondary to abnormal transport of chloride and sodium across the epithelium. In the lung, this leads to the development of thick, tenacious secretions that obstruct the airways and submucosal glands, which in turn leads to chronic bacterial infection and inflammation, as described above.

Management of CF has been focused primarily on the treatment of CF lung disease with antibiotics and with other therapies directed at optimizing airway clearance.[1] Improved nutrition has also played a vital role in prolonging survival of CF patients.[3] Until recently, there have been no therapies available that directly address the underlying CFTR defect in CF patients. Pharmacological compounds that are intended to correct mutation-specific functional defects in the CFTR protein have been under active investigation. Four of these therapies, ivacaftor (KALYDECO®, Vertex Pharmaceuticals Inc.), ivacaftor combined with lumacaftor (ORKAMBI®, Vertex Pharmaceuticals Inc.), ivacaftor combined with tezacaftor (SYMDEKO®, Vertex Pharmaceuticals Inc.), and ivacaftor combined with elexacaftor and tezacaftor (TRIKAFTA®, Vertex Pharmaceuticals Inc.) have shown clinical benefit in trials and have been recently approved in the US for patients with the specific targeted gene mutations (Section 1.3.2).

Newborn screening for CF is now routinely performed in the US and in Europe in the United Kingdom, France, Italy, Spain, Austria, Poland, and the Czech Republic as well as in Australia and New Zealand.[12,13] The screening methodology incorporates measurement of immunoreactive trypsinogen on dried blood spots as a first step, followed by either repeat immunoreactive trypsinogen testing and/or DNA testing for CF mutations as a second step.[12] Sweat testing is then performed to confirm a diagnosis of CF.

1.2. Overview of MRT5005

The ultimate treatment goal is to restore CFTR function in the lungs of all CF patients, irrespective of the patient's underlying CFTR gene mutation. One approach has been the insertion of a normal copy of the CFTR DNA gene into affected cells by gene therapy. Since 1993, more than 25 clinical studies have been conducted using adenovirus, adeno-associated virus serotype 2, or non-viral vectors to deliver the CFTR DNA gene to the upper and/or lower respiratory tract of CF patients.[14] Unfortunately, this approach has proven to be difficult and has yielded disappointing results.[14,15]

An alternative to DNA gene therapy is the delivery of a CFTR-encoding messenger RNA (mRNA) directly into affected cells, bypassing the need for the CFTR DNA gene to enter the cell nucleus to be transcribed into mRNA. The CFTR-encoding mRNA would express CFTR protein instantly once it reached the cytoplasm of the cell. There are many other advantages of an

mRNA-based therapy as compared to DNA gene therapy, particularly with respect to safety.[16] In contrast to DNA, mRNA cannot integrate into the genome, which excludes the possibility of insertional mutagenesis, and without CpG motifs, has reduced immunogenic effects. In addition, as mRNA has a limited half-life, levels of the expressed protein can be controlled more precisely by dose and dosing frequency, which is an important consideration for both safety and efficacy of the therapy. There are a number of mRNA-based cancer immunotherapies and infectious disease vaccines that have entered clinical development.[17]

MRT5005 is a new molecular entity and first-in-class pharmaceutical agent, which has been designed to restore CFTR function in the lungs of CF patients by respiratory delivery of mRNA encoding for the wild-type human CFTR protein. Once delivered to the surface of the respiratory epithelium, cellular uptake and translation of the mRNA would then result in the expression of normally functioning CFTR protein and restoration of CFTR chloride channel activity in the lungs. MRT5005 takes advantage of cationic lipid-based nanoparticle technology to deliver the mRNA to the target bronchial epithelial cells. Lipid nanoparticles containing ionizable cationic lipids represent the most promising non-viral vectors for delivering DNA and RNA.[18–22]

The active drug substance of MRT5005 is a biosynthetic [redacted] mRNA ([redacted] mRNA), which encodes for the normal human CFTR protein. [redacted] and several elements within the [redacted] mRNA structure were incorporated to promote activity through increased stability and enhanced translation by the ribosome. [redacted] mRNA is formulated with an [redacted] lipid nanoparticle ([redacted] LNP) as the vehicle to deliver [redacted] mRNA to the lungs. The primary component of the [redacted] LNP is the cationic lipid [redacted], which is mixed with two other non-cationic lipids, [redacted] in the formation of the lipid nanoparticle (LNP). Complexed within the [redacted] LNP, [redacted] mRNA is protected from degradation and can be delivered by aerosol to the respiratory tract. The lipid nanoparticle facilitates penetration of the airway mucus layer, uptake by the target bronchial epithelial cells, and release of [redacted] mRNA into the cytoplasm. The coding region of [redacted] mRNA subsequently undergoes translation and produces the desired normal human CFTR protein. The newly expressed CFTR protein is processed and trafficked to its normal site in the apical plasma membrane where it is intended to restore CFTR chloride channel activity at the epithelial cell surface of the lung. MRT5005 is delivered in the form of an aerosol, administered to the lungs by a vibrating mesh nebulizer commonly used in medical practice. Additional information on MRT5005 can be found in the Investigator's Brochure.

Study MRT5005-101 represents an important first step in the evaluation of mRNA therapy as an approach to restoring CFTR function in the lungs of CF patients. The goal was to design a single study that could achieve both Phase 1 and 2 objectives while ensuring subject safety. This Phase 1/2, first-in-human study will evaluate the safety and tolerability of single and multiple escalating doses of MRT5005 administered by nebulization to the respiratory tract of adult subjects with CF. This study will also characterize its biological activity by measuring changes in $ppFEV_1$ and other spirometry parameters post-treatment.

1.3. Indication and Current Treatment Options

1.3.1. Indication for MRT5005

The intended indication for MRT5005 is for the treatment of patients with cystic fibrosis.

1.3.2. Current Treatment Options for Cystic Fibrosis

Treatment options for CF have been primarily supportive. The main focus of CF treatment is the control and prevention of pulmonary infections with antibiotics. Other therapies are directed at optimizing airway clearance and the management of CF-related gastrointestinal disease. Antibiotic therapies fall into 3 categories: regimens to delay colonization of the lungs by P. aeruginosa; chronic maintenance antibiotics to reduce the frequency and morbidity of pulmonary exacerbations (eg, inhaled tobramycin); and treatment of pulmonary exacerbations with intravenous antibiotics for 2 to 3 weeks. Other therapies directed at airway clearance include inhaled treatments with mucolytics (recombinant human deoxyribonuclease I [rhDNase, dornase alfa, PULMOZYME®]), hypertonic saline, and bronchodilators; inhaled and systemic therapy with anti-inflammatory agents; and chest physiotherapy. For pancreatic insufficiency, CF patients are treated with pancreatic enzyme supplements and multivitamins to maintain adequate nutrition.

Four therapies are available that target the underlying CFTR defect in CF patients. These pharmacological compounds are intended to correct mutation-specific functional defects in the CFTR protein. Ivacaftor is approved for the treatment of CF patients with certain Class III (eg, G551D) and Class IV (eg, R117H) gene mutations (KALYDECO, Vertex Pharmaceuticals, Inc.). These 38 mutations account for approximately 15% of CF cases in the US.[23] Ivacaftor combined with lumacaftor is approved for the treatment CF patients who are homozygous for the F508del mutation in the CFTR gene (ORKAMBI, Vertex Pharmaceuticals, Inc.) Ivacaftor combined with tezacaftor is approved for the treatment of CF patients who are homozygous for the F508del mutations or at least one of 26 (mostly Class IV and Class V) specified mutations (SYMDEKO, Vertex Pharmaceuticals Inc.). Patients who are homozygous for the F508del mutations account for 45.3% of CF cases in the US.[5] Ivacaftor combined with tezacaftor (SYMDEKO®, Vertex Pharmaceuticals, Inc.) is approved for the treatment of CF patients who are homozygous for the F508del mutations or who have at least one of 26 (mostly Class IV and Class V) specified mutations. A triple-combination CFTR modulator therapy (TRIKAFTA, Vertex Pharmaceuticals, Inc.) recently received marketing approval in the US and has expanded the coverage of CFTR mutations to approximately 90% of CF patients. Nonetheless, there remains a significant unmet need for the approximately 10% of CF patients whose mutations are non-amenable to CFTR modulators.

1.4. Product Background

A description of MRT5005 is provided in Section 1.2 and in Section 6.1. Information on study drug preparation and management is provided in Section 6.2.2.

Additional information on MRT5005 can be found in the Investigator's Brochure.

1.4.1. Preclinical Information

The results of the nonclinical studies conducted with MRT5005 are summarized below. More detailed information on these studies and their results can be found in the MRT5005 Investigator's Brochure.

1.4.1.1. Proof-of-Concept Pharmacology Studies

Nonclinical pharmacology studies have demonstrated in vitro production and functionality of human CFTR protein following transfection of HEK293T and Fischer rat thyroid cells with [redacted] mRNA. Following transfection with increasing amounts of [redacted] mRNA, a dose-dependent increase in human CFTR protein expression was observed in both cell lines and a dose-dependent increase in functional ion channel activity was observed in Fischer rat thyroid cells based on Ussing chamber measurements.

In vivo pharmacological activity of MRT5005 has been explored in a CFTR knock-out [$CFTR^{tm1Unc(Tg\text{-}FABP)}$] mouse model, as well as in normal mice. The pharmacological activity of MRT5005 was also examined as part of non-GLP and GLP-compliant toxicology studies in normal rats and non-human primates (cynomolgus monkeys). These studies have demonstrated that aerosol administration of single and multiple doses of MRT5005 (five once weekly doses) resulted in a dose-dependent deposition of [redacted] mRNA in the lungs of treated animals at levels that were orders of magnitude higher than the endogenous levels of wild type CFTR mRNA (up to 1500-fold higher). [redacted] mRNA was found to be broadly distributed throughout the lungs and was detected in bronchial epithelial cells as well as in alveolar regions.

More importantly, widespread expression human CFTR protein was observed in the lungs of treated animals. Consistent with the deposition of [redacted] mRNA, human CFTR protein production was detected in both bronchial epithelial as well as alveolar regions of the lungs. Furthermore, dose-dependent increases in human CFTR protein were observed after both single and multiple dose administrations of MRT5005 in rats and non-human primates, and human CFTR protein was found to persist for up to 28 days after treatment at the higher doses.

1.4.1.2. Pharmacokinetic Studies

The active substance of MRT5005, [redacted] mRNA, is a high molecular weight biomolecule (approximately 1630 kD) and therefore is expected to be transported across lung epithelia and into blood only to a limited degree. This is what has been observed in both rats and non-human primates. As a result, dedicated pharmacokinetic studies of [redacted] mRNA were not performed, but instead biodistribution and toxicokinetics were examined as part of non-GLP and GLP-compliant toxicology studies in rats and non-human primates.

The MRT5005 pharmacokinetic/toxicokinetic data have been generated from the following toxicology studies: a single-dose, dose range-finding toxicity study in non-human primates; and GLP multiple-dose inhalation toxicity studies in rats and non-human primates treated with 5 once weekly doses of MRT5005.

The results show high levels of [redacted] mRNA in lung tissue and associated respiratory tract tissues such as larynx, trachea, tracheobronchial lymph nodes, and nasal turbinates with very low

or background levels in heart, brain, liver, kidney, spleen, testis, and ovary. Lung tissue levels were high and dose-responsive in both rats and non-human primates. Blood levels of [redacted] mRNA were very low and variable, preventing a reliable analysis of toxicokinetic parameters.

The toxicokinetics of [redacted] LNP were also examined using an assay that could measure [redacted] lipid in the blood. There were no measurable levels of [redacted] lipid in whole blood post-treatment with MRT5005. There were, however, measurable and dose-responsive levels of [redacted] lipid in the lung tissue of both rats and non-human primates treated with MRT5005.

An analysis of the kinetics of lung clearance of [redacted]mRNA in rats indicated a single component exponential decay with a half-life of approximately 2-3 days. Lung clearance of [redacted]mRNA was less reliably determined in non-human primates as only two data points were available; however, these data appeared to be consistent with the rat data when the differences in dose were taken into account.

1.4.1.3. Toxicology Studies

The nonclinical program has characterized MRT5005 in a standard battery of safety pharmacology and toxicity studies. MRT5005 has been evaluated in the following safety studies: 1) GLP inhalation safety pharmacology study in rats (cardiovascular evaluation); 2) single-dose, dose range-finding toxicity study in non-human primates; and 3) GLP multiple-dose inhalation toxicity studies in rats and non-human primates treated with 5 once weekly doses of MRT5005.

All toxicology studies with MRT5005 have resulted in no adverse effects up to the highest achievable dose levels. MRT5005 was well tolerated at all doses tested. There were no clinical signs associated with treatment, and there were no clinically important effects on cardiovascular and respiratory parameters (heart rate; ECG rhythm and intervals; respiration rate, tidal volume, and derived minute volume), body temperature, clinical pathology, and macroscopic and microscopic pathology. Importantly, there were no histopathologic effects in the respiratory tract that were considered adverse following repeated exposure to MRT5005 at all dose levels tested up to the maximum achievable dose.

Based on the absence of adverse effects at any of the dose levels tested of MRT5005, the no-observed-adverse-effect-levels (NOAELs) are the maximum inhaled doses for each study. In the GLP multiple-dose inhalation toxicity studies, the maximum doses tested in rats and non-human primates were 6.70 mg/kg and 0.69 mg/kg, respectively.

1.4.2. Clinical Information

Study MRT5005-101 will be the first evaluation of MRT5005 in human subjects.

1.5. Risk/Benefit and Ethical Assessment

At this early stage in the development of MRT5005, the benefits of MRT5005 therapy remain to be established. As such, there are no known or expected benefits for the CF subjects participating in this study in relation to the investigational product (IP) MRT5005. However, their

participation may contribute to the development of a new therapy that could provide significant clinical benefit for CF patients in the future.

Adult CF patients were selected as the first subjects to receive MRT5005, as the balance between the anticipated risks and potential benefits of the study were judged as acceptable for adult patients with CF and unfavorable for healthy volunteers. The ability to detect and interpret the activity of MRT5005 in CF patients, either adverse or beneficial, was an important consideration in the selection of CF patients as the clinically relevant population for the study. In addition, due to the potential for persistent effects resulting from the treatment (eg, immunogenicity of the expressed protein), the risk-benefit profile was considered unacceptable for healthy volunteers.

As this will be the first human exposure to MRT5005, potential risks associated with MRT5005 treatment will be mitigated through the following study elements:

- There will be an extensive safety follow-up of all subjects in the study. All subjects will be monitored for safety for 12 months (48 weeks) after administration of the last dose of IP (post-single dose in Part A; post-fifth dose in Parts B and D).

- The exposure to MRT5005 will be limited to a single dose in Part A and to 5 total doses in Part B (administered 1 dose per week for 5 weeks) of the study. The exposure to MRT5005 in Part D will be also limited to 5 total doses (administered as 1 dose per day for 5 consecutive days) at a dose strength that is equivalent to a single well-tolerated weekly dose divided over 5 days. After each dose, the exposure to [redacted] mRNA, the active drug substance of MRT5005, and the resulting translated CFTR protein is expected to be transient with half-lives estimated to be 14 and 29 hours, respectively.[24,25]

- In Parts A and B of the study, a dose escalation design, with staggered enrollment and treatment of subjects within the dose group, will be utilized to minimize risk to subjects. The enrollment and treatment of subjects within each dose group will be staggered by at least 1 week (Part A) or 2 weeks (Part B), with the exception of the 12 mg dose group in Part B which will not have staggered enrollment under the circumstances described in Section 3.1.

  The Protocol Safety Review Committee (PSRC) will have oversight of the dose escalation process; the safety data from each of the dose groups will be reviewed by the PSRC to determine if escalation to the next higher dose level can proceed safely (Section 3.4). The PSRC will also conduct a safety data review before initiation of enrollment and treatment of subjects in the MAD groups in Part B. (Section 3.4.3).

- Safety-related stopping criteria are defined and will be employed in the study (Sections 4.5.4, 4.5.5, and 4.5.6).

- Women of childbearing potential are eligible to participate in the study. The study design includes measures to minimize the possibility of fetal exposure to the IP (Section 4.4.1). The informed consent will provide female subjects with sufficient

information so that they may make informed decisions about the potential risks and benefits of the therapy and the study.

As part of the safety evaluation, assays to detect immune responses to CFTR protein post-treatment will be performed (Section 7.5.2.15). In addition to the time points specified in the schedule of assessments, immunogenicity testing will also be performed when immunogenicity is suspected, such as allergy/hypersensitivity events or unexplained bronchospasm.

Based on the risk mitigation elements discussed above, in combination with the knowledge that will be gained on MRT5005 as a potential therapeutic for CF lung disease, Translate Bio believes that the risk-benefit balance of this study is acceptable for adult CF subjects.

2. STUDY OBJECTIVES AND PURPOSE

Study objectives are provided in Section 2.3. Study endpoints are provided in Section 2.4.

2.1. Rationale for the Study

Therapy with MRT5005 is intended to correct the underlying CFTR defect in the lungs of CF patients by delivering human CFTR-encoding mRNA into affected cells, which can then be translated into normal functioning CFTR protein. This approach is supported by nonclinical proof-of-concept studies, which demonstrated that aerosol delivery of MRT5005 leads to a dose-dependent deposition of [redacted] mRNA in the lungs of animals and subsequent expression of human CFTR protein (Section 1.4.1.1).

Study MRT5005-101 is a Phase 1/2, first-in-human evaluation of MRT5005 as a novel mRNA-based therapeutic approach for treating CF lung disease. Study objectives and endpoints are provided in Section 2.3 and Section 2.4.

Study MRT5005-101 was designed to evaluate the safety, tolerability, and biological activity of nebulized MRT5005 in CF subjects. The results of this study will guide dose selection for all future Phase 2 and 3 clinical studies in CF subjects.

2.2. Rationale for Study Design, Study Population, and Dose Selection

2.2.1. Study Design

Study MRT5005-101 is a Phase 1/2, first-in-human trial that is designed to achieve both Phase 1 and 2 objectives while ensuring subject safety. The objectives and endpoints of the study are described in Section 2.3 and Section 2.4.

Study MRT5005-101 is designed as a randomized, double-blind, placebo-controlled, combined single and multiple ascending dose (SAD and MAD) trial, which will be conducted in 3 parts. Subjects will be administered single and multiple escalating doses of MRT5005 in Parts A and B of the study, respectively. Multiple dosing in Part B will consist of 5 doses of MRT5005, administered 1 dose per week for 5 consecutive weeks. In Part D, subjects will be administered 4 mg of MRT5005 or placebo administered as 1 dose per day for 5 consecutive days.

The overall design of the study is shown in Appendix 1. The rationale behind the selection of the dose levels to be investigated is discussed in Section 2.2.3.

In all 3 parts of the study, subjects will be randomized to receive either MRT5005 or placebo (normal saline) in a 3:1 ratio. Blinded, placebo-treated subjects are included in the study to facilitate interpretation of the safety and tolerability data, and to provide controls for assessing the delivery of [redacted]mRNA and its biological activity as reflected by changes in CFTR protein levels and CFTR chloride channel activity. Study MRT5005-101 will be conducted at a limited number of study centers, so that safety can be monitored effectively across all participating subjects, and decisions with respect to dosing and dose escalation can be performed efficiently. A PSRC will have responsibility for the overall safety of the subjects participating in

the study, and will have oversight of the dose-escalation process and decisions to initiate Part B of the study (Section 3.4.1).

This study is primarily intended to assess the safety and tolerability of single and multiple escalating doses of nebulized MRT5005. The 8 mg dose level of MRT5005 will be the SAD starting dose in Part A, followed by sequential escalation to the 16 mg and 24 mg dose levels of MRT5005. An additional 20 mg dose level will be evaluated in Part A resulting from the observation of febrile reactions in 3 of 4 subjects treated in the 24 mg single dose level. The 8 mg dose level of MRT5005 will be the MAD starting dose in Part B, followed by sequential escalation to the 16 mg and 20 mg dose level of MRT5005. An additional 12 mg dose level will be evaluated in Part B. In both Parts A and B of the study, 4 groups consisting of 4 subjects each will receive single or multiple doses of MRT5005 or placebo at a 3:1 ratio. Part B subjects will receive 5 doses of IP, administered 1 dose per week for 5 weeks.

The dose escalation design in Parts A and B will incorporate staggered enrollment and treatment of the subjects within each dose group to minimize risks to subjects. Within each dose group, the enrollment and treatment of the 4 subjects will be staggered by at least 1 week in Part A and by at least 2 weeks in Part B (the next subject in the Part B dose group will only be enrolled and treated when the previous subject has received their second dose and there is approximately 1 week of safety follow-up). Under the circumstances described in Section 3.1, the 12 mg multiple dose group in Part B may not require staggered enrollment. When the specified safety follow-up has been performed for the fourth subject in the dose group, and no dose limiting toxicity has been observed and there are no safety concerns for the dose group overall, the enrollment and treatment of subjects at the next higher dose level will be initiated. Dose escalation criteria are further described in Section 3.4.

Part C (bronchoscopy groups) was removed from the protocol in the 3rd amendment to the protocol (Version 4.0 dated 29 July 2019).

Part D was added to the protocol (Version 5.0 dated 30 July 2020) and will evaluate the safety and tolerability of daily dosing over 5 consecutive days. Eight subjects in Part D will be randomized in a 3:1 ratio to receive 5 consecutive daily doses of either 4 mg MRT5005 or placebo. Enrollment and treatment of subjects will not be staggered in Part D.

As assessment of safety is the primary outcome of the study, an extended safety follow-up for each of the subjects will be performed. All subjects in the study will be monitored for safety for 12 months (48 weeks) after administration of the last dose of IP (post-single dose in Part A; post-fifth dose in Parts B and D). The safety and tolerability of nebulized MRT5005 will be assessed based on the types, frequency, and severity of treatment-emergent adverse events (AEs) reported as well as on the results of a standard battery of clinical procedures and tests. As part of the safety evaluation, assays to detect [redacted] mRNA and [redacted] in the blood post-treatment will be performed along with assays to detect immune responses to CFTR protein or anti-PEG antibodies.

2.2.2. Study Population

Adult CF subjects with mild to moderate disease were selected as the first subjects to receive MRT5005, as the risk to benefit ratio was judged as acceptable for this patient population (Section 1.5). Inclusion and Exclusion criteria are described in Section 4.1 and Section 4.2 .

Male and female adult subjects with CF will be enrolled into the study. Subjects will have clinically stable disease with an FEV_1 ≥50% and ≤90% predicted, which represents moderate to mild disease. As this is the first human exposure to MRT5005, patients with severe lung disease were excluded. Subjects with a comorbidity that would pose an additional risk from the IP or study procedures were also excluded.

Eligibility will be limited to those patients with 2 severe CF disease-causing CFTR mutations in Class I or II. Patients with these classes of mutations express very little to no mature functional CFTR protein, which will increase the ability to detect MRT5005-mediated increases in CFTR protein levels and chloride channel activity assessed in the secondary endpoints of the study.

Although exploratory in nature, the secondary endpoint is still viewed as an important proof-of-concept evaluation of MRT5005 therapy. Therefore, CF patients who have the potential of confounding the evaluation of the secondary endpoint, because their mutations result in residual levels of CFTR protein and/or CFTR function, will be excluded from the study as described below.

- Patients with a Class III, IV, or V CFTR gene mutation in at least 1 allele will be excluded from the study. Patients with Class III and IV mutations produce normal quantities of CFTR protein but with reduced function due to defective channel gating or conductance. In contrast, patients with Class V mutations express reduced quantities of CFTR protein, which function normally. Patients with Class IV or V mutations typically have a milder CF phenotype due to residual CFTR function.

  Note: As the phenotype and classification of some CFTR mutations remains uncertain, the eligibility of a patient with one of these mutations will be at the discretion of the Investigator and Sponsor, based on the patient's medical history.

- Patients with Class III and IV mutations will also be excluded on the basis of receiving ivacaftor monotherapy, which can potentiate CFTR chloride channel activity.

- Patients with one or more unclassified mutations will be evaluated on a case-by-case basis to determine whether the mutation(s) confers partial CFTR function in the opinion of the Investigator and Sponsor. The Parts B and D Coordinating Investigator will adjudicate eligibility of unclassified mutations as needed.

Patients who are receiving treatment with lumacaftor/ivacaftor or tezacaftor/ivacaftor combination drugs (ORKAMBI or SYMDEKO) will not be excluded from the study. It was felt that these therapies would not significantly interfere with the evaluation of the secondary endpoint based on their modest effect on CFTR protein levels and function, as determined in vitro and in vivo.[25,26] Patients who are receiving treatment with ivacaftor monotherapy

(KALYDECO) will be excluded because KALYDECO is not approved for use in patients with Class I or Class II mutations. For Parts A and B only, elexacaftor/tezacaftor/ivacaftor triple combination therapy (TRIKAFTA) will be excluded because of the potential of this therapy to confound the evaluation of the secondary endpoint. Subjects in Parts A and B who are eligible for TRIKAFTA may switch/start on TRIKAFTA; however, subjects must not start/switch until at least 2 months after their last dose of study drug so as not to confound the interpretation of the primary and secondary endpoints. Patients who are receiving treatment with TRIKAFTA will not be excluded from Part D of the study.

Women of childbearing potential may participate in the study based on the rationale that CF disease is serious and affects women. The study design includes measures to minimize the possibility of fetal exposure to the IP. This consists of pregnancy testing prior to participation in the study and the use of an acceptable form of contraception if the subject is sexually active during the course of the study (Section 4.4.1). Females of childbearing potential currently taking the lumacaftor/ivacaftor combination drug (ORKAMBI) and using oral hormonal contraceptives will be required to take an additional or alternative method of contraception to prevent pregnancy in this study. The informed consent provides female subjects with sufficient information so that they may make informed decisions about the potential risks and benefits of the therapy and the study.

2.2.3. Dose Selection

The maximum dose to be evaluated in study MRT5005-101 was established from nonclinical toxicology studies using lung exposure in animals, expressed as mg of [redacted]mRNA deposited in the lung per g of lung weight, as the basis for dose determination in human subjects. This approach assumes that the lung will be the main site for any potential adverse effects associated with inhaled MRT5005, which is dosed based on its active drug substance [redacted] mRNA. Using this approach, a 10-fold margin of safety means that the animal NOAEL calculated on the basis of deposited dose per g of lung is 10-fold greater than the estimated human deposited dose per g of lung.

The no-observed-adverse-effect-level (NOAEL), expressed as inhaled dose of [redacted] mRNA in mg per kg body weight, was determined for both rats and non-human primates (cynomolgus monkeys) in GLP 29-day toxicity studies. In these studies, animals were exposed to 5 doses of MRT5005 (weekly dosing), which was administered to the respiratory tract using an Aerogen Solo vibrating mesh nebulizer similar to the InnoSpire Go nebulizer to be used in this study. (The InnoSpire Go and Aerogen Solo utilize the same Aerogen vibrating mesh for aerosol generation.)

It is important to note that both of the NOAELs were observed at the maximum feasible dose for both species, ie no adverse effects were observed for MRT50005 in either species up to the maximum inhaled dose achieved in the studies. Because of the ability to expose rats for a longer period of time than non-human primates (6 vs. 2 hours), a higher maximum dose and therefore NOAEL was achieved in rats than in non-human primates. The longer exposure and higher dose enabled a more thorough assessment of potential toxicity in rats. Based on the much higher maximum feasible dose achieved in rats combined with the sensitivity of this species to the

adverse effects of an earlier polymer-based hCFTR mRNA formulation and to other inhaled agents in general,[27,28] the NOAEL observed in the GLP 29-day rat study was used to determine the maximum clinical dose to be evaluated in this first-in-human Phase 1/2 study.

As shown in Table 10, the NOAEL in rats was determined to be 6.70 mg/kg, which corresponds to a deposited lung dose of 0.134 mg of [redacted] mRNA per g lung weight. For non-human primates, the NOAEL was determined to be 0.69 mg/kg, which corresponds to a deposited lung dose of 0.024 mg of [redacted] mRNA per g lung weight (see footnote b in Table 10 for calculations of the deposited lung doses from the NOAELs.[29,30]

Table 10 Basis for Human Dose Determination

	Repeat-Dose Toxicity Studies			Clinical Study MRT5005-101	
	NOAEL[a] (mg [redacted] mRNA/kg body wt)	**Deposited Lung Dose[b]** (mg [redacted] mRNA/g lung wt)	**Human Equivalent Dose (HED)[c]** (mg [redacted] mRNA)	**Maximum Dose** (mg [redacted] mRNA)	**Safety Factor**
Rats	6.70 mg/kg	0.134 mg/g lung	268.0 mg	24.0 mg	11.2x
Non-human Primates	0.69 mg/kg	0.024 mg/g lung	48.0 mg	24.0 mg	2.0x

[a] NOAEL: No-observed-adverse-effect-level. NOAEL is expressed as the inhaled dose in mg [redacted] mRNA per kg body weight.

[b] Rat - The deposited lung dose was calculated by multiplying the NOAEL inhaled dose (mg/kg) by an assumed body weight of 0.3 kg for rats, and then multiplying by 0.1 assuming a 10% deposition in the lung. The deposited dose (mg) was then divided by a typical lung weight of 1.5 gm for a 0.3 kg rat, to obtain a deposited dose on a lung weight basis.

Non-human primate - The deposited lung dose was calculated by multiplying the NOAEL inhaled dose (mg/kg) by an assumed body weight of 3 kg for non-human primates, and then multiplying by 0.25 assuming a 25% deposition in the lung. The deposited dose (mg) was then divided by a typical lung weight of 22 g for a 3 kg non-human primate, to obtain a deposited dose on a lung weight basis.

[c] The human equivalent dose (nominal dose) was calculated by multiplying the deposited lung dose (mg/g lung weight) for both rats and non-human primates by an assumed lung weight of 1000 g for a 60 kg human subject, and then dividing by 0.5 assuming a 50% deposition of the dose in the lung from an InnoSpire Go nebulizer.

The deposited lung doses for the NOAELs were then converted to human equivalent doses (HEDs) expressed as mg of [redacted] mRNA (nominal dose). Assuming a lung weight of 1000 g for a 60 kg human subject and 50% deposition of the dose in the lung from an InnoSpire Go nebulizer, the HEDs were calculated by first multiplying the NOAEL deposited lung dose by 1000, and then dividing by 0.5 (see footnote c in Table 10). Deposition from an Aerogen Solo nebulizer used in clinical settings (identical Aerogen vibrating mesh as in the InnoSpire Go) has been found to be 16% to 26% and, as such, 50% deposition represents a conservative value.[31,32] HEDs of 268.0 and 48.0 mg of [redacted] mRNA were determined, respectively, from the rat and non-human primate NOAELs.

For the reasons stated above, the NOAEL established in the rat study was used to determine the maximum clinical dose. As such, a safety margin of at least 10 was applied to the HED of the rat

NOAEL. Although the achieved exposure of non-human primates was much lower, it was still desirable to have the clinical dose meet a minimum safety margin of at least 2 relative to the HED of the non-human primate NOAEL.

The MRT5005 dose containing 24 mg of [redacted] mRNA was selected as the highest dose to be evaluated in study MRT5005-101. As shown in Table 10, this dose fulfills the desired safety margin criteria: it exceeds the safety factor of 10 based on the HED derived from the rat NOAEL and also provides an added assurance of safety based on a safety factor of 2.0 relative to the HED derived from the non-human primate NOAEL. Two dose levels lower than the 24 mg dose level, 8 and 16 mg, were then chosen as part of the dose escalation strategy. The rationale for the dose range was based on i) escalation from a safe starting dose of 8 mg, which represents safety margins of 33.5 and 6.0 relative to the HEDs derived from the rat and non-human primate NOAELs, respectively, and ii) exploration of a range of doses that possess biological activity as determined in the nonclinical studies.

The 8, 16, and 24 mg human doses provide lung exposures (0.004, 0.008, and 0.012 mg of [redacted] mRNA deposited per g lung, respectively) that are comparable to those of the lower doses given to the rats and non-human primates in the single and multiple-dose toxicity studies (0.19 to 0.77 mg/kg dose levels corresponding to 0.0065 to 0.0154 mg of [redacted] mRNA deposited per g lung, and calculated HEDs of 13 to 31 mg). These dose levels deposited significant levels of [redacted] mRNA in the lungs of both species compared to endogenous levels and, importantly, expressed detectable levels of human CFTR protein by immunohistochemistry at 24 hours post-treatment. Persistence of the human CFTR protein was also detected in rats at 7 days post-treatment following a single dose of MRT5004 at 0.53 mg/kg (HED of 22 mg); and at 28 days post-treatment following 5 once weekly doses of MRT5005 at 0.77 mg/kg (HED of 31 mg). These observations supported the dose levels and weekly dosing interval of MRT5005 that will be investigated in Parts A and B of this study.

The 4 mg dose strength was selected for evaluation in Part D based on observations of mild to moderate febrile reactions reported in 7 subjects who received a single dose of MRT5005 ranging from 8 to 24 mg (1 subject each in the 8 mg, 16 mg, 20 mg single dose groups in Part A, 3 subjects in the 24 mg single dose group in Part A, 1 subject in the 16 mg multiple dose group in Part B who discontinued treatment after first dose). Evaluation of a lower dose will help determine whether febrile reactions associated with MRT5005 are dose dependent or idiosyncratic. Investigation of a daily dosing regimen in Part D is attractive given the estimated short half-life of CFTR mRNA (14 hours) and translated CFTR protein (29 hours). The anticipated safety of 4 mg administered daily for 5 days (20 mg total) can be predicted from the safety and tolerability of 20 mg administered as a single dose in Part A.

2.3. Study Objectives

2.3.1. Primary Objective

To evaluate the safety and tolerability of single and multiple escalating doses of MRT5005 administered by nebulization to adult subjects with CF.

2.3.2. Secondary Objective

The secondary objective of the study is to evaluate the effect on percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and other spirometry parameters after single and multiple escalating doses of MRT5005 administered by nebulization to adult subjects with CF.

2.4. Study Endpoints

2.4.1. Primary Endpoint

The safety and tolerability of nebulized MRT5005 will be assessed based on the types, frequency, and severity of treatment-emergent AEs including pulmonary exacerbations; concomitant medication use; and changes from baseline in physical examination, weight, vital signs, oxygen saturation (pulse oximetry), ECG, standard clinical laboratory tests, chest x-ray, and spirometry as a measure of pulmonary function.

2.4.2. Secondary Endpoint

The biological activity of nebulized MRT5005 will be assessed based on changes from baseline in $ppFEV_1$ and other spirometry parameters.

3. STUDY DESIGN

3.1. Overall Study Design and Plan

The study will be conducted at multiple centers in the US with expertise in treating CF patients. At least 40 adult male and female patients with CF, 18 years of age or older, are planned to participate in the study. Patients who are clinically stable with an FEV_1 ≥50% and ≤90% predicted, and who meet all inclusion criteria and none of the exclusion criteria will be eligible for the study. Women of childbearing potential will also be eligible to participate if they are willing and able to comply with contraception requirements.

This Phase 1/2 study is designed as a randomized, double-blind, placebo-controlled, combined single and multiple ascending dose (SAD and MAD) trial, which will be conducted in 3 parts. Subjects will be administered single and multiple escalating doses of MRT5005 in Parts A and B of the study, respectively. In Part D, subjects will be administered 5 consecutive daily doses of 4 mg MRT5005 or placebo.

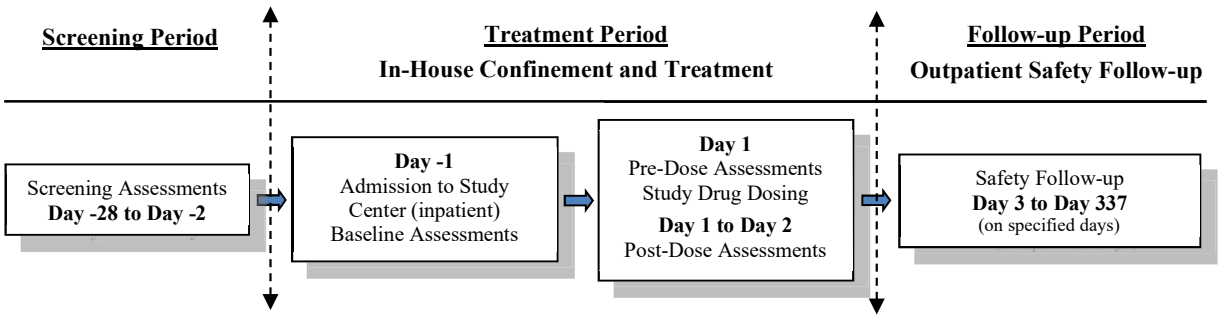
If subjects do not complete the study or complete certain procedures, additional subjects will be enrolled at the Sponsor's discretion to ensure that at least 16, 16, and 8 evaluable subjects complete Parts A, B, and D of the study, respectively (Section 3.3). As described in Section 3.3, an additional group of new subjects may be enrolled and treated in Part A, with up to a maximum of 44 evaluable subjects participating in the study.

As shown in Figure 1, each part of the study will consist of a screening period, a treatment period, and a follow-up period. Multiple visits during the screening period, from Day -28 to Day -2 (Parts A and B) or from Day -28 to Day -1 (Part D), may be necessary for the subject to complete all of the required screening procedures and tests. During the treatment period, subjects participating in Part A will be confined to the study center from Day -1 to Day 2 and will receive a single dose of IP. This will be followed by a safety follow-up period, which continues up to the final study visit on Day 337. During the safety follow-up, clinic visits for Part A subjects will be performed on an outpatient basis.

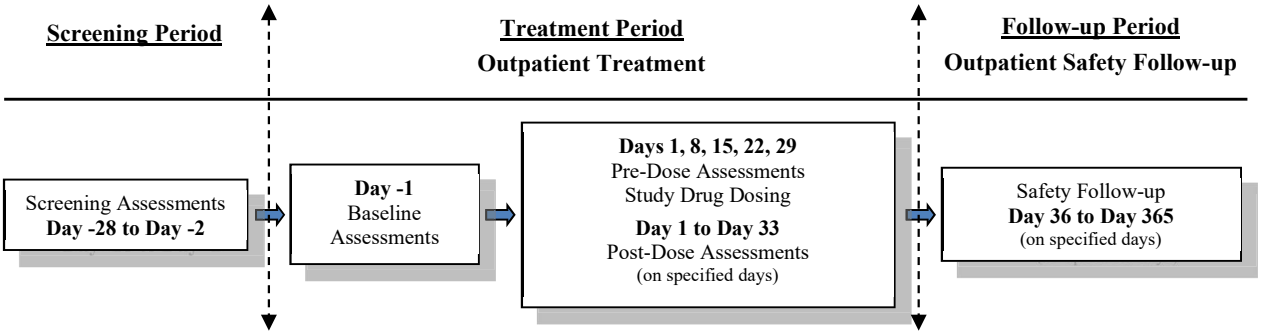
No confinement will be required of subjects in Parts B and D of the study; these subjects will perform all clinic visits in the treatment and follow-up periods as outpatients. During the treatment period of Part B (Day -1 to Day 33), subjects will receive 5 doses of IP, administered 1 dose per week for 5 weeks. During the treatment period of Part D (Day 1 to Day 5), subjects will receive 5 doses of IP, administered 1 dose per day for 5 days. The safety follow-up period will continue up to the last study visit on Day 365 for Part B and Day 341 for Part D.

Figure 1: Study Design Flow Chart

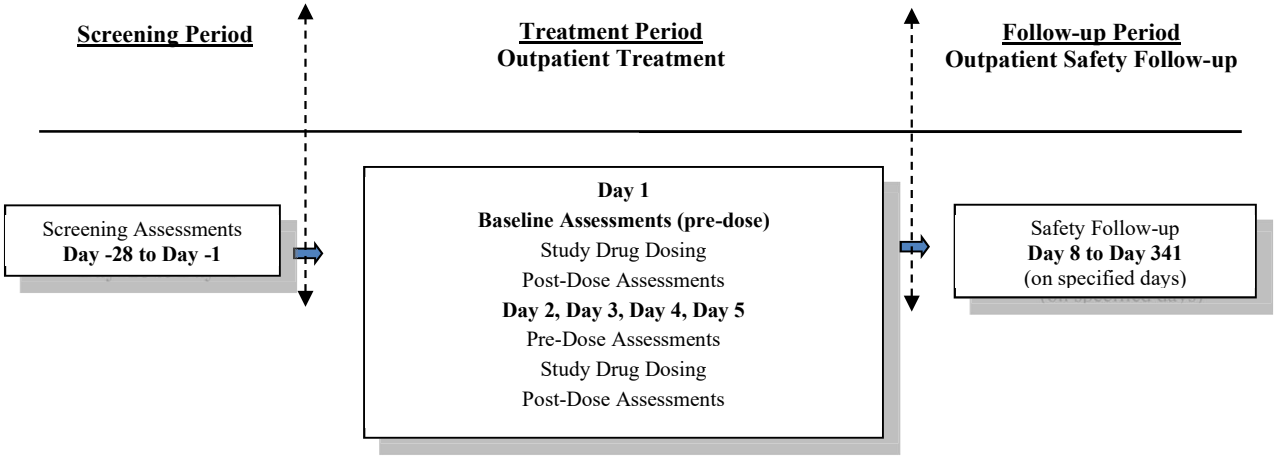
Part A



Part B



Part D



See Table 1 through Table 9 for the schedule of procedures and tests to be performed during each of the 3 periods in Parts A, B, and D of the study. Flow diagrams of subject enrollment and treatment allocation are presented in Appendix 1.

In Part A (SAD groups), 4 groups consisting of 4 subjects each will be enrolled sequentially to receive single doses of MRT5005 or placebo (normal saline) administered by nebulization. Three dose levels of MRT5005 were planned to be investigated: 8, 16, and 24 mg of [redacted] mRNA (the active drug substance of MRT5005; nominal dose). An additional treatment group (20 mg) was added after blinded safety information from the 24 mg dose group revealed the occurrence of febrile reactions in 3 of 4 subjects. Within each dose group, the enrollment and treatment of the 4 subjects will be staggered by at least 1 week. Subjects will be randomized in a 3:1 ratio to receive a single dose of either MRT5005 or placebo (3 subjects to receive MRT5005 and 1 subject to receive placebo per dose group). For details on subject enrollment and treatment allocation for Part A, see Section 3.2.1.

The PSRC will be responsible for reviewing safety data and, based on this review, making the decision to dose escalate from the 8 mg starting SAD dose level to the 16 mg dose level, and then to the 24 mg maximum dose level. The 20 mg dose level will be evaluated after the 24 mg dose level. The dose escalation process for Part A is described in detail in Sections 3.2.1 and 3.4.2.

The decision to begin enrollment and treatment of the initial 8 mg multiple-dose group in Part B will also be made by the PSRC, based on a review of at least 28 days of safety follow-up for all subjects who received a single dose of the 8 mg dose level in Part A. The initiation of enrollment and treatment of subjects in Part B is described in Sections 3.2.2 and 3.4.3.

In Part B (MAD groups), 4 groups consisting of 4 subjects each will receive multiple doses of MRT5005 or placebo administered by nebulization. Three groups will be enrolled sequentially to receive dose levels of MRT5005 investigated as single doses in Part A (8 mg, 16 mg, and 20 mg). An additional dose level that was not investigated in Part A (12 mg) will also be evaluated in Part B. The 12 mg dose group may be enrolled in parallel with the 16 and/or 20 mg dose group. Within each dose group, subjects will be randomized in a 3:1 ratio to receive 5 doses of either MRT5005 or placebo (3 subjects to receive MRT5005 and 1 subject to receive placebo per dose group), administered 1 dose per week for 5 weeks. The enrollment and treatment of the 4 subjects within the 8 mg, 16 mg, and 20 mg dose groups will be staggered by at least 2 weeks (the next subject in the dose group will only be enrolled and treated when the previous subject has received their second dose and there is approximately 1 week of safety follow-up). The enrollment and treatment of the 4 subjects within the 12 mg dose group may occur in a staggered or non-staggered fashion depending on the timing of the PSRC review of the 16 mg multiple dose group data, as follows:

- Staggered enrollment and treatment will be required if the 12 mg multiple dose group starts enrolling prior to the PSRC meeting to review the 16 mg multiple dose data.

- Non-staggered enrollment and treatment is acceptable after the PSRC has reviewed the 16 mg multiple dose data and deemed the 16 mg multiple dose level was well tolerated.

- If the PSRC meeting to review the 16 mg multiple dose group occurs while the 12 mg dose group is open for enrollment, all subjects who enroll after the PSRC has met and deemed the 16 mg dose level was well tolerated may be enrolled and treated in a non-staggered fashion.

Similar to Part A, the PSRC will be responsible for reviewing safety data and making the decision to dose escalate. The dose escalation process for Part B is described in detail in Sections 3.2.2 and 3.4.2.

In Part D, 8 subjects will be randomized in a 3:1 ratio to receive 5 doses of either 4 mg MRT5005 or placebo, administered at 1 dose per day for 5 consecutive days.

Because single doses up to 20 mg, as well as 5 weekly doses up to 16 mg have been tolerated in Parts A and B, the enrollment and treatment of the 8 subjects within Part D will not be staggered.

All subjects in the study will be monitored for safety for 12 months after administration of the last dose of IP (post-single dose in Part A; post-fifth dose in Parts B and D). The safety and tolerability of nebulized MRT5005 will be assessed based on the types, frequency, and severity of treatment-emergent AEs reported including the number of pulmonary exacerbations; concomitant medication use; and changes from baseline in physical examination, weight, vital signs, oxygen saturation (pulse oximetry), electrocardiogram (ECG), standard clinical laboratory tests, chest x-ray, and spirometry as a measure of pulmonary function. As part of the safety evaluation, assays to detect [redacted] mRNA and [redacted] in the blood post-treatment will be performed along with assays to detect antibody and T cell immune responses to CFTR protein and anti-PEG antibodies.

This will be conducted as a double-blind study, except for the last part of the 12 months follow-up. All subjects in the study will be followed for 12 months after their last dose, but the treatment randomization for the 8 mg, 16 mg, and 24 mg single dose groups will be unblinded 1 month after the last dose of the last subject in the 24 mg single dose group in Part A. The blind will be maintained in the 20 mg single dose group in Part A, as well as the 8, 16, and 12 mg multiple dose groups in Part B until the 1-month timepoint after the last dose (Day 57) of the last subject dosed in the 12 mg dose group. For the 20 mg multiple dose group in Part B (if applicable), the blind will be maintained until the last subject in this group has reached the 1-month timepoint after the last dose day (Day 57). For Part D, the blind will be maintained until the 1-month timepoint after the last dose (Day 32) of the last subject in Part D.

During the double-blind period, the Investigators and all study staff involved in the evaluation of subject eligibility and assessment of the study outcomes will be blinded to treatment assignment (MRT5005 vs. placebo within each dose group). All subjects and their families, as well as Sponsor personnel in direct contact with the study center, will also be blinded (Section 6.1.3).

3.2. Subject Enrollment and Treatment Allocation

Subjects will be recruited from multiple CF centers in the US. Forty male and female patients with CF, 18 years of age or older, are planned to participate in the study. This will be a 3-part study with 16 subjects participating in Part A; 16 subjects participating in Part B; and 8 subjects participating in Part D.

Subjects will not be allowed to participate in more than 1 part of the study.

At the initial screening visit, informed consent will be obtained from the subject. A unique subject identification number will then be assigned, which will serve as the subject's identifier throughout the study and in the case report form (CRF). Subjects in Parts A and B will be randomized to treatment and thereby enrolled in the study after the following 2 conditions have been met:

1. Subject meets all of the inclusion criteria and none of the exclusion criteria during the screening period and Day -1.

2. Confirmation of eligibility on Day 1. Results from the Day -1 and pre-dose tests on Day 1 (AE, conmeds, pulse oximetry, physical exam, vital signs) do not reveal a new safety issue making the subject ineligible for randomization. A subject is considered enrolled into the study when he or she has been randomized to treatment. Pre-dose tests that may occur after randomization but MUST occur and be reviewed by the PI prior to first dose include spirometry and ECG. If the pre-dose Day 1 ECG or spirometry results reveal a safety issue making it inadvisable to administer the dose to the randomized subject, then the subject will be considered an Early Discontinuation.

Subjects in Part D will be randomized to treatment and thereby enrolled in the study after the following 2 conditions have been met:

1. Subject meets all of the inclusion criteria and none of the exclusion criteria during the screening period.

2. Confirmation of eligibility on Day 1 prior to randomization. Results from the Day 1 pre-dose assessments (AE, conmeds, pulse oximetry, physical exam, vital signs, pregnancy test [female subjects only]) do not reveal a new safety issue making the subject ineligible for randomization. A subject is considered enrolled into the study when he or she has been randomized to treatment.

The PSRC will be responsible for reviewing safety data and, based on this review, making decisions to dose escalate in Parts A and B, and to initiate enrollment and treatment of subjects in Parts B. See Section 3.4.1 for a description of the PSRC and its responsibilities.

Subject enrollment and treatment allocation are described below and flow diagrams for the 3 parts of the study are provided in Appendix 1.

3.2.1. Part A

See Appendix 1, Part A, for a flow diagram

Three groups consisting of 4 subjects each will be enrolled sequentially to receive single escalating doses of IP. Within each dose group, subjects will be randomized to receive a single dose of either MRT5005 (in mg of [redacted] mRNA; nominal doses) or placebo (normal saline) in a 3:1 ratio. The treatment groups, which will be studied in the order presented, will be as follows:

- Group 1 (N=4): 3 subjects randomized to receive a single dose of 8 mg of MRT5005 and 1 subject randomized to receive a single dose of placebo.
- Group 2 (N=4): 3 subjects randomized to receive a single dose of 16 mg of MRT5005 and 1 subject randomized to receive a single dose of placebo.
- Group 3 (N=4): 3 subjects randomized to receive a single dose of 24 mg of MRT5005 and 1 subject randomized to receive a single dose of placebo.

The 8 mg dose level will be the starting SAD dose, followed by sequential escalation to the 16 mg and 24 mg dose levels of MRT5005.

An additional treatment group was added after blinded safety information from Group 3 revealed the occurrence of febrile reactions in 3 of 4 subjects. The additional treatment group will be as follows:

- Group 4 (N=4): 3 subjects randomized to receive a single dose of 20 mg of MRT5005 and 1 subject randomized to receive a single dose of placebo.

The enrollment and treatment of the 4 subjects within each dose group will be staggered by at least 1 week. When 1 week of safety follow-up has been performed for the fourth subject in the dose group (applies to Groups 1 and 2), blinded safety data for the 4 subjects in the group will be reviewed by the PSRC. If no dose limiting toxicity has been observed and there are no safety concerns for the dose group overall, the enrollment and treatment of subjects at the next higher dose level will be initiated (see Section 3.4.2 for dose-escalation criteria for Part A and definition of dose limiting toxicity).

Based on the judgment of the PSRC, a Part A dose group may be repeated in a new group of subjects to further assess the safety of the dose level before escalating to the next higher dose level or before multiple dosing is allowed to proceed in Part B. The enrollment and treatment of the 4 new subjects in the repeated dose group will continue to be staggered by at least 1 week to minimize risks to subjects. Subjects will also continue to be randomized in a 3:1 ratio to receive a single dose of either MRT5005 or placebo.

3.2.2. Part B

See Appendix 1, Part B, for a flow diagram

The 8 mg dose level of MRT5005 will be the MAD starting dose in Part B. The decision to begin enrollment and treatment of the first MAD group will be made by the PSRC, based on a review of at least 28 days of safety follow-up for all subjects who received a single dose of the 8 mg dose level in Part A (see Section 3.4.3 for criteria to initiate enrollment and treatment in Part B). If no dose limiting toxicity has been observed and there are no safety concerns for the single-dose group overall, the enrollment and treatment of subjects in the first MAD group at the 8 mg dose level will be initiated.

Three groups consisting of 4 subjects each will be enrolled sequentially to receive multiple doses of IP. Within each dose group, subjects will be randomized to receive 5 doses of either MRT5005 (in mg of [redacted]mRNA; nominal doses) or placebo (normal saline) in a 3:1 ratio. The 5 doses of IP will be administered 1 dose per week for 5 weeks. The treatment groups will be as follows:

- Group 1 (N=4): 3 subjects randomized to receive 5 doses of 8 mg of MRT5005 and 1 subject randomized to receive 5 doses of placebo.
- Group 2 (N=4): 3 subjects randomized to receive 5 doses of 16 mg of MRT5005 and 1 subject randomized to receive 5 doses of placebo.
- Group 3 (N=4): 3 subjects randomized to receive 5 doses of 20 mg of MRT5005 and 1 subject randomized to receive 5 doses of placebo.

The 8 mg dose level will be followed by sequential escalation to the 16 mg and 20 mg dose levels of MRT5005.

An additional treatment group was added to explore the safety profile at an intermediate dose level that was not investigated as a single dose in Part A as follows:

- Group 4 (N=4): 3 subjects randomized to receive 5 doses of 12 mg of MRT5005 and 1 subject randomized to receive 5 doses of placebo.

After the PSRC deems the 8 mg dose level to have been well-tolerated and approves dosing at the 16 mg dose level, the 12 mg dose level may begin enrollment in parallel with the 16 mg dose level. The enrollment and treatment of the 4 subjects within each MAD dose group will be staggered by at least 2 weeks (the next subject in the dose group will only be enrolled and treated when the previous subject has received their second dose and there is approximately 1 week of safety follow-up), with the exception of the 12 mg dose group in Part B which may not require staggered treatment under the circumstances described in Section 3.1.

Escalation from the 8 mg to the 16 mg and 12 mg, and from the 16 mg to the 20 mg multiple dose group in part B will occur after review of the following safety data by the PSRC:

1. At least 1 week of safety follow-up after the 3rd dose of the 4th (last) subject of the previous (lower) dose.

2. At least 28 days of safety follow-up after the dose of the 4th (last) subject of the corresponding single ascending dose cohort in Part A. Note that there is no corresponding single dose cohort for the 12 mg multiple dose group and therefore this requirement is not applicable.

For instance, for the decision to escalate from the 8 mg dose group to the 16 and 12 mg multiple dose group, the PSRC will review at least 7 days of safety follow-up after the 3rd dose of the 4th (last) subject receiving multiple doses of 8 mg, as well as at least 28 days of safety follow-up after the single dose of the 4th (last) subject receiving a single dose of 16 mg.

Similar to Part A, if no dose limiting toxicity has been observed and there are no safety concerns for the dose group overall, the enrollment and treatment of subjects at the next higher dose level will be initiated (see Section 3.4.2 for dose-escalation criteria and definition of dose limiting toxicity).

3.2.3. Part D

Eight subjects will be randomized in a 3:1 ratio to receive 5 doses of either 4 mg MRT5005 at or placebo, administered at 1 dose per day for 5 consecutive days. Based on the safety experience gained in Parts A and B, the enrollment and treatment of the 8 subjects in Part D will not be staggered. During the treatment of subjects in Part D, should AEs occur that indicate the study drug is not tolerated well, the enrollment and treatment of subjects may be terminated by the PSRC and Sponsor, and enrollment and treatment of a lower dose strength may be considered in the remaining subjects in the cohort . For example, if the tolerability of the 4 mg daily dose level is found to be unacceptable, then the 2 mg dose level can be considered for investigation.

3.3. Planned Number of Subjects

At least 40 male and female subjects with CF, 18 years of age or older, are planned to participate in the study. If subjects do not complete either certain procedures or the study, additional subjects will be enrolled at the Sponsor's discretion to ensure that at least 16, 16, and 8 evaluable subjects complete Parts A, B, and D of the study, respectively (see Section 4.5.2).

Potential changes in the planned number of subjects are summarized as follows:

- Although dose escalations are planned in each of Parts A and B, escalation to the next higher dose level may not occur if dose limiting toxicity is encountered at the current dose level. Therefore, the number of subjects and groups required to complete the dose escalation sequences in either the SAD or MAD parts of the study may be fewer than planned.

- A SAD dose group may be repeated in a new group of subjects in Part A to further assess the safety of the dose level before escalating to the next dose level, or before allowing it to proceed from Part A (SAD) to Part B (MAD).

It is expected that no more than 1 additional group of 4 subjects will be enrolled into the study in Part A. Therefore, up to a maximum of 44 evaluable subjects may participate in the study. If this

subject number is to be exceeded, the Investigators will notify their IRBs and a justification for enrolling beyond 44 subjects will be provided.

3.4. Criteria for Dose-Escalation in Parts A and B / Criteria for Initiation of Part B

3.4.1. Protocol Safety Review Committee (PSRC)

3.4.1.1. Composition and Responsibilities

A PSRC will be formed and will have responsibility for the overall safety of the subjects participating in the study; and will have oversight of the dose-escalation process and decisions to initiate Part B of the study. The PSRC will be composed of the following members:

- Medical Monitor
- Coordinating Investigators
- An independent CF clinical expert
- Independent DMC Chair from the Cystic Fibrosis Foundation Therapeutic Development Network (CFF TDN)

The PSRC will conduct a safety data review before each dose-escalation in Parts A and B and before initiation of enrollment and treatment of subjects in the first MAD group in Part B. Based on these safety data reviews, the PSRC will decide whether to proceed at each of these time points in the study.

Based on the judgment of the PSRC:

- A Part A dose group may be repeated in a new group of subjects to further assess the safety of the dose level before escalating to the next higher dose level or before multiple dosing is allowed to proceed in Part B (see Section 3.2.1).

Safety data reviews will be based on unmonitored data at the time a review takes place. Blinded safety data reports will include a listing of the AEs and clinical laboratory test results for the dose group as well as any other relevant clinical data. To facilitate review of the data, the PSRC may request unblinding the treatment assignment(s) for an individual subject or for an entire dose group, as described below in Sections 3.4.2 and 6.2.3.

The members of the PSRC, which includes the Medical Monitor, coordinating Investigators, the DMC Chair from the Cystic Fibrosis Foundation Therapeutics Development Network, and independent CF clinical expert, will review the safety data blinded.

After each safety data review by the PSRC, all decisions will be documented in writing and must include the following:

- List of participants
- A summary of the data considered
- A summary of the decision, including any concerns which were raised
- The final decision, stating that the decision was agreed upon by the PSRC

In the absence of a principal/coordinating Investigator, decisions may be delegated in writing to a medically qualified sub-Investigator at the coordinating Investigator's study center, on the provision that this is in agreement with Translate Bio.

Each decision must be confirmed in writing (scanned copy via email or fax is acceptable) to the other members of PSRC and study Investigators by the Medical Monitor before the escalated dose level is administered to subjects in Part A or Part B, or before initiating Part B of the study.

The Study Investigators will have the responsibility to ensure that IRBs are notified in writing of any changes from the planned escalation sequence in Parts A and B, or of any changes from the planned initiation of Part B of the study. In the event that a dose group is repeated in Part A, dosing will occur concurrently with the submission of the notification to the IRB.

3.4.1.2. Other Oversight Roles

The PSRC will have responsibility for the overall safety of the subjects participating in the study as well as for making key decisions in the conduct of the study. These are summarized below. All decisions by the PSRC must be documented in writing.

The PSRC will be notified of 2 occurrences of significant febrile reactions in different participants (defined as ≥ Grade 2 fever [>39.0°C] associated with systemic symptomatology [eg, body aches, malaise, nausea]) within 24 hours following administration of IP. The PSRC will also be notified of all serious adverse events deemed possibly, probably, or definitely related to investigational product in real-time and will receive treatment-emergent SAE listings following each dose group and may choose to receive more frequent SAE listings at any time during the study.

If dose group stopping criteria described in Section 4.5.4 or Part D stopping criteria described in Section 4.5.5 are met during the study, the relevant data will be reviewed by the PSRC. Following this review, the PSRC will decide whether the dose group and other ongoing higher dose groups will continue or be terminated.

If study stopping criteria are met during the study, all available data relating to the safety of the IP will be reviewed by the PSRC. Following this review, the PSRC will decide whether the study will continue or be terminated (Section 4.5.6).

If an adverse event of special interest (AESI), as described in Section 8.1.8, is reported during the study, the PSRC will be notified by the Sponsor in real-time.

To ensure subject safety, the PSRC may request unblinding the treatment assignment(s) for an individual subject or for an entire dose group.

For example, if IP administration is halted based on the stopping criteria of the study, the subsequent safety review may necessitate unblinding a subject's treatment assignment; or the safety data for an individual subject or the dose group may be unblinded before making the decision to dose escalate (eg, to determine if a treatment-emergent AE occurred in a placebo subject or not).

If there are any tolerability issues identified at the current single or multiple dose level (eg, tolerability of the prolonged nebulization time as the dose escalates), the PSRC, which includes the coordinating Investigators of the study, will ensure that the other Investigators and next group of subjects enrolled at the next higher dose level are informed of the issues.

During the treatment of subjects in Part D, should AEs occur that are not tolerated well, the enrollment and treatment of subjects may be terminated by the PSRC and Sponsor, and enrollment and treatment of a lower dose level may be considered (Section 3.2.3).

The PSRC's data review will include review of the immunogenicity data, where available, to determine whether there is any association with allergy/hypersensitivity events, pulmonary exacerbations, and decreased pulmonary function.

3.4.2. Dose Escalation Criteria for Parts A and B

In Part A of the study, the 4 dose groups will be enrolled sequentially; the enrollment and treatment of the 4 subjects within each dose group will be staggered by at least 1 week. When 1 week of safety follow-up has been performed for the fourth subject in the group (Groups 1 and 2), the PSRC will review the blinded safety data for the 4 subjects in the group to determine if escalation to the next higher dose level (single dose) can proceed. If no dose limiting toxicity has been observed and there are no safety concerns for the dose group overall, the enrollment and treatment of subjects at the next higher single-dose level will be initiated.

In Part B of the study, the 8, 16, and 20 mg dose groups will be enrolled sequentially. The 12 mg dose group may be enrolled in parallel with the 16 and/or 20 mg dose group. The enrollment and treatment of the 4 subjects within each dose group will be staggered by at least 2 weeks (the next subject in the dose group will only be enrolled and treated when the previous subject has received their second dose and there is approximately 1 week of safety follow-up), with the exception of the 12 mg dose group in Part B which may not require staggered treatment under the circumstances described in Section 3.1.

Escalation from the 8 mg to the 16 and 12 mg, and from the 16 mg to the 20 mg multiple-dose group in Part B will occur after review of the following safety data by the PSRC:

1. At least 1 week of safety follow-up after the 3rd dose of the 4th (last) subject of the previous (lower) dose.

2. At least 28 days of safety follow-up after the dose of the 4th (last) subject of the corresponding single ascending dose cohort in Part A. Note that there is no corresponding single dose cohort for the 12 mg multiple dose group and therefore this requirement is not applicable.

For instance, for the decision to escalate from the 8 mg dose group to the 16 mg multiple dose group, the PSRC will review at least 7 days of safety follow-up after the 3rd dose of the 4th (last) subject receiving multiple doses of 8 mg, as well as at least 28 days of safety follow-up after the single dose of the 4th (last) subject receiving a single dose of 16 mg.

When the fourth subject in the dose group (Groups 1 and 2) has completed at least 1 week of safety follow-up after the third dose, the PSRC will review the blinded safety data for the 4 subjects in the group. The PSRC will also review the blinded safety data for the Part A subjects who received a single dose of the next higher dose level to be escalated to. Similar to Part A, if no dose limiting toxicity has been observed and there are no safety concerns for the dose group overall, the enrollment and treatment of subjects at the next higher dose level will be initiated.

In both Parts A and B of the study, escalation to the next higher dose level may not proceed if 2 or more subjects at the current dose level experience a Grade 3 (severe) treatment-emergent AE that is assessed as both clinically significant (based on the nature and duration of the toxicity) and probably or definitely related to IP by the Investigator. The PSRC will review these treatment-emergent AEs along with all available safety data to determine if dose escalation can proceed or will be stopped due to dose limiting toxicity. Other scenarios, which include but are not limited to the occurrence of possibly related Grade 3 (severe) treatment-emergent AEs, or probably or definitely related Grade 2 (moderate) treatment-emergent AEs that are judged as clinically significant, will be reviewed and assessed on a case-by-case basis by the PSRC.

If deemed necessary by the PSRC, a dose group may be repeated in a new group of subjects to further assess the safety of the dose level prior to dose escalation in Part A or to further assess the tolerability of the dose level before deciding to advance it from single dosing in Part A to multiple dosing in Part B (see below).

The PSRC may request unblinding the treatment assignment(s) for an individual subject or for the entire dose group to help clarify decisions to dose escalate, to repeat a dose group, or to initiate Part B (Section 6.2.3).

3.4.3. Criteria to Initiate Enrollment and Treatment in Part B

The 8 mg dose level of MRT5005 will be the MAD starting dose in Part B. The decision to begin enrollment and treatment of the first MAD group will be made by the PSRC, based on a review of at least 28 days of safety follow-up for all subjects who received a single dose of the 8 mg dose level in Part A. The review will take into consideration the clinical significance of the treatment-emergent AEs reported during the period (based on the nature, severity, and duration of the AE), and their relationship to IP (includes any available safety data from subjects who received a single dose of the higher 16 mg dose level in Part A).

If no dose limiting toxicity has been observed and there are no safety concerns for the single-dose group overall, the enrollment and treatment of subjects in the first MAD group at the 8 mg dose level will be initiated.

3.5. Duration and Study Completion Definition

The subject's maximum duration of participation is summarized below.

- Planned maximum duration of study participation in Part A: up to 368 days. This consists of an initial screening period of up to 27 days, followed by 338 days (+3 day window) of the treatment and follow-up periods of the study.

- Planned maximum duration of study participation in Part B: up to 396 days. This consists of an initial screening period of up to 27 days, followed by 366 days (+3-day window) of the treatment and follow-up periods of the study.

- Planned maximum duration of study participation in Part D: up to 372 days. This consists of an initial screening period of up to 28 days, followed by 341 days (+ 3-day window) of the treatment and follow-up periods of the study.

The study completion date is defined as the date the last subject completes their final protocol-defined assessment. The study completion date is used to determine the timing for study results posting and reporting.

3.6. Sites and Regions

This study will be conducted at multiple centers in the US.

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed.

4.1. Inclusion Criteria

Patients will not be considered eligible for the study without meeting all of the inclusion criteria below. Patients cannot be enrolled before all inclusion criteria (including test results) are confirmed.

1. Male and female patients with CF, 18 years of age or older.
2. Confirmed diagnosis of CF as defined by both of the following:
   - Two CF disease-causing CFTR mutations in Class I or II (genotype confirmed at the screening visit). CFTR genotyping will only be performed if adequate prior documentation is not available.
   - Chronic sinopulmonary disease and/or gastrointestinal/nutritional abnormalities consistent with CF disease.
3. Clinically stable CF disease, as judged by the Investigator.
4. FEV_1 ≥50% and ≤90% of the predicted normal for age, gender, and height at screening.
5. Resting oxygen saturation ≥92% on room air (pulse oximetry).
6. Body mass index ≥17.5 kg/m^2 and weight ≥40 kg at screening.
7. Willing to remain on stable CF medications for the duration of the study.
   - Patients who are receiving lumacaftor/ivacaftor or tezacaftor/ivacaftor combination drugs (ORKAMBI or SYMDEKO) are eligible for the study; however, patients must have been on stable treatment with this medication for at least 28 days prior to the screening visit, and should remain on it for the duration of the study preferably at a stable dose.
8. Non-smoking for a minimum of 2 years.
9. Willing and able to give written, signed, and dated informed consent to participate in the study.
10. Willing and able to comply with scheduled visits, treatment, laboratory tests, restrictions, contraception requirements (Section 4.4), and other study procedures.
    - Patients must have adequate clinical condition to safely undergo the planned study procedures.
    - Able and willing to receive nebulized IP through a mouthpiece for up to 133 minutes.

4.2. Exclusion Criteria

Patients will be excluded from the study if any of the following exclusion criteria are met. Patients cannot be enrolled before it is determined that the patient does not meet any of the exclusion criteria (including test results).

1. History of any comorbidity that, in the opinion of the Investigator, could confound the results of the study, pose an additional risk from the IP or study procedures, could potentially contribute to the clinical instability of the subject during the study, or would make the subject unlikely to complete the study. This may include, but is not limited to a history of cardiovascular, renal, or central nervous system disease; history of serious mental illness; history or presence of clinically significant pathology including liver cirrhosis and/or portal hypertension; and history of uncontrolled CF-related diabetes.

2. An acute upper or lower respiratory infection, pulmonary exacerbation, or clinically significant episode of hemoptysis (>30 mL or in the opinion of the Investigator) within 28 days prior to Day 1.
3. Any of the following changes in medication prior to Day 1:
   - Any change in chronic respiratory medication within 28 days prior to Day 1.
   - Initiation of any new chronic therapy (eg, inhaled hypertonic saline, or inhaled antibiotic (tobramycin [TOBI], aztreonam [CAYSTON]) within 28 days prior to Day 1.
   - Use of antibiotics or oral steroids for acute symptoms within 14 days prior to Day 1.
4. Receiving treatment with ivacaftor monotherapy (KALYDECO).
5. Parts A and B only: Receiving treatment with triple combination therapy (TRIKAFTA). Patients with a prior history of treatment with TRIKAFTA are eligible to participate if treatment has been discontinued at least 28 days prior to Day 1.
6. Patients with a Class III, IV, or V CFTR gene mutation in at least 1 allele.
   - See Appendix 2 for guidance on the classification of CFTR mutations. (As the phenotype and classification of some CFTR mutations remains uncertain, the eligibility of a patient with 1 of these mutations will be at the discretion of the Investigator and Sponsor, based on the patient's medical history).
7. Any of the following abnormal laboratory values at screening:
   - Hemoglobin <10 g/dL.
   - Serum albumin <2.5 g/dL.
   - Abnormal liver function defined as meeting any 3 or more of the following: ALT >3x upper limit of normal (ULN); AST >3x ULN; GGT >2.5x ULN; alkaline phosphatase >2.5x ULN; and total bilirubin >1.5x ULN (except for patients with isolated Gilbert Syndrome).

8. Any clinically significant abnormal laboratory test result prior to Day 1 that would interfere with the study assessments or indicate clinical instability of the patient, as judged by the Investigator.
9. Infection with highly virulent bacteria associated with accelerated decline in pulmonary function and/or decreased survival (eg, Burkholderia cenocepacia, Burkholderia dolosa, Mycobacterium abscessus). For a patient with a history of positive culture, he/she can be considered free of infection based on the following guidance:
    - All cultures obtained within the past 12 months should be negative for these bacteria. The patient should have had at least 2 cultures performed within the past 12 months, at least 3 months apart, with at least 1 culture obtained within 6 months of screening for this study.
10. History of or listed for solid organ or hematological transplantation.
11. Positive viral serology test results for HIV type 1 or 2 antibodies, hepatitis B surface antigen (HBsAg), or hepatitis C virus (HCV) antibodies at screening.
12. Positive test for drugs of abuse or alcohol at the screening visit.
13. Donation of blood or blood products within 60 days prior to the initial screening visit.
14. Participation in an IP or device study within 30 days prior to the initial screening visit or at any time during this Translate Bio-Sponsored study. (The 30-day window applies to IPs with elimination half-lives of <6 days. If the elimination half-life of the IP is ≥6 days, then the window should be extended to at least 5 half-lives from the last dose administered.)
15. Prior enrollment in this study, with the exception of subjects who discontinued treatment after one dose of study drug for a reason unrelated to safety as specified in Section 7.1.1.2. (A patient is considered enrolled into the study when he or she has been randomized.)
16. Any suspicion of, or history of, alcohol and/or other substance abuse or addiction within the past year.
17. Pregnant or lactating females.
18. History of drug allergy or other allergy that, in the opinion of the Investigator, contraindicates participation (eg, history of allergic reactions that could interfere with the safety assessment of the IP).
19. History of allergic reactions to any component of the IP including its excipients.

4.3. Restrictions

The following restrictions apply to the in-house stay in the study center (Day -1 to Day 2) for subjects participating in Part A of the study.

1. Subjects should refrain from strenuous physical exercise 48 hours prior to admission to the study center and during the in-house stay at the study center.

2. Subjects should refrain from alcohol 48 hours prior to admission to the study center and during the in-house stay at the study center.

3. Subjects will be required to eat the provided meals while housed in the study center.

4.4. Reproductive Potential

4.4.1. Female Contraception

Sexually active females of childbearing potential should be using an acceptable form of contraception. These subjects must be advised to use an acceptable method of contraception, as defined below, from the time the informed consent is signed until the final study visit on Day 337 (±3 days) in Part A, Day 365 (±3 days) in Part B, or Day 341 (±3 days) in Part D of the study. If hormonal contraceptives are used, they should be administered according to the package insert.

Females of childbearing potential who are not currently sexually active must agree to use an acceptable method of contraception, as defined below, if they become sexually active during the study.

Acceptable methods of contraception are:

- Intrauterine devices plus condoms.

- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam).

- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the administration of the IP, plus condoms. Note: if a subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

- Females of childbearing potential currently taking the lumacaftor/ivacaftor combination drug (ORKAMBI) and using oral hormonal contraceptives will be required to take an additional or alternative method of contraception to prevent pregnancy in this study.

- Vasectomized partner (at least 6 months post-procedure).

- Exclusively same-sex (female) partner.

Female subjects of non-childbearing potential are defined as either:

- Post-menopausal (12 consecutive months of spontaneous amenorrhea and ≥51 years of age)

  or

- Surgically sterile (having undergone one of the following procedures: hysterectomy, bilateral tubal ligation, bilateral oophorectomy, or bilateral salpingectomy) and at least 6 weeks post-sterilization.

Serum or urine β-hCG pregnancy tests will be performed on all female subjects, regardless of childbearing potential, as described in Section 7.5.2.8.

4.4.2. Male Contraception

All sexually active male subjects who are able to have children must agree to consistently use a barrier method from the time the informed consent is signed until the final study visit on Day 337 (±3 days) in Part A, Day 365 (±3 days) in Part B, or Day 341 (±3 days) in Part D of the study. Female partners of these subjects must also use at least one of the acceptable methods of contraception listed in Section 4.4.1 during the same time period.

Male subjects who are able to have children must agree not to donate sperm for the purposes of making a woman pregnant from the time the informed consent is signed up to the final study visit.

For this study, male subjects will be considered as unable to have children if they are 1) infertile due to congenital bilateral absence of the vas deferens documented in the subject's medical record based on ultrasonography and/or semen analysis, 2) sterilized (vasectomy), 3) not sexually active, or 4) exclusively same sex (male) partner.

4.5. Discontinuation of Subjects and Individual Stopping Rules

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The Investigator is encouraged to discuss withdrawal of a subject with the Medical Monitor when possible.

If a subject is discontinued from the study, regardless of the reason, the early withdrawal evaluations listed below are to be performed as completely as possible. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for termination must be recorded in the CRF and source documents (Section 4.5.1).

If enrolled subjects discontinue from the study, these subjects may be replaced at the Sponsor's discretion, as described in Section 4.5.2.

Early withdrawal evaluations:

- Physical examination
- Vital signs (blood pressure, pulse, body temperature, respiratory rate)
- Pulse oximetry
- Weight
- Spirometry
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis, C-reactive protein [CRP])
- ECG
- AE/serious adverse event (SAE) reporting
- Recording of concomitant medications and concomitant surgical procedures
- Serum or urine pregnancy test
- Testing for immune response assays, inflammatory markers, and/or [redacted] mRNA and [redacted] assays at the discretion of the Investigator and/or Sponsor

4.5.1. Reasons for Discontinuation and Individual Stopping Rules

Individual Subjects will be discontinued by the Investigator if they meet any of the stopping rules described below:

1. A significant febrile reaction defined as ≥ Grade 2 fever (>39.0 °C) associated with systemic symptomatology (eg, body aches, malaise, nausea) within 24 hours following administration of IP.
2. An absolute decrease in predicted FEV1 of at least 25% compared to the baseline value (defined as the average of the Day -1 and Day 1 pre-dose values) during the 5-week treatment period in Part B or through Day 11 (1 week post-5th dose) in Part D that cannot be explained, in the opinion of the PI, by the underlying disease of CF and that is confirmed on 2 separate occasions at least 3 days apart
3. A suspected moderate to severe allergic/hypersensitivity reaction, including but not limited to anaphylaxis, generalized rash, edema or bronchospasm possibly related to drug treatment
4. Deterioration of liver function as explained below and in Section 8.1.4.1
   a. Elevation of ALT or AST to >5x ULN in a subject regardless of baseline value
   b. Elevation of ALT or AST to >3x ULN in a subject with a normal baseline or elevation of >3x ULN from the subject's actual baseline if not normal, with the

appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

c. Elevation of ALT or AST to >3x ULN in a subject with a normal baseline or elevation of >3x ULN from the subject's actual baseline if not normal, and total bilirubin >2x ULN or INR >1.5.

If any of the above criteria is met by a Part B or Part D subject who has not completed dosing with IP, treatment must be interrupted immediately and the Medical Monitor notified of this action.

A thorough investigation of other potential causes should be conducted in all cases. If no convincing alternative etiology (eg, pre-existing CF-related liver disease, viral hepatitis, alcohol ingestion, concomitant medication [such as antibiotic treatment]) for the elevated transaminases and symptoms is identified, regardless of whether ALT or AST levels have improved, treatment of the subject must be discontinued, in consultation with the Medical Monitor. If a convincing alternative etiology for the elevated transaminases is identified and the subject's symptoms and laboratory findings have improved, the Investigator may consider resuming IP treatment with close monitoring, in consultation with the Medical Monitor.

The reason for withdrawal must be determined by the Investigator and recorded in the subject's medical record and on the CRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the CRF.

Reasons for discontinuation include but are not limited to:

- AE
- Pregnancy
- Protocol deviation
- Withdrawal by subject
- Lost to follow-up
- Physician decision
- Study terminated by Sponsor
- Other (if "Other" is selected, the Investigator must specify on the CRF)

For all discontinued subjects who received the IP, every attempt must be made to follow each subject for the duration of the study.

4.5.2. Replacement of Subjects

If the planned number of subjects do not complete the study or complete certain procedures, additional subjects will be enrolled at the Sponsor's discretion to ensure that at least 16, 16, and 8 evaluable subjects complete Parts A, B, and D of the study, respectively.

4.5.3. Subjects Lost to Follow-up Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the final scheduled study visit on Day 337 (±3 days) in Part A, Day 365 (±3 days) in Part B, or Day 341 (±3 days) in Part D of the study. At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the study center for their final safety evaluations.

4.5.4. Dose Group Stopping Criteria

IP administration will be halted for all subjects in a dose group, as well as any subjects in an ongoing higher dose group if any of the following stopping criteria are met:

a. Two subjects in a dose group experience a significant febrile reaction (defined as ≥ Grade 2 fever [>39.0 °C] associated with systemic symptomatology [eg, body aches, malaise, nausea]) within 24 hours following administration of IP.

b. Two subjects in a dose group experience a suspected moderate to severe allergic/hypersensitivity reaction, including but not limited to anaphylaxis, generalized rash, edema or bronchospasm possibly related to drug treatment.

To determine whether this dose group stopping rule has been met, the relevant data will be reviewed by the PSRC. The treatment assignment of one or more subjects may be unblinded at the request of the PSRC, as described in Section 3.4.1.2. Following this review, the PSRC will decide if the dose group and other ongoing higher dose groups will:

- Resume unchanged or
- Resume with modifications to the protocol or
- Be terminated.

The Sponsor is responsible for notifying the relevant regulatory authorities and the Investigator is responsible for promptly notifying the relevant IRB of the decision.

4.5.5. Part D Stopping Criterion

IP administration will be halted for all subjects in Part D if the following stopping criterion is met:

a. Three subjects experience Grade 1 fevers (38.0 to 39.0 °C) associated with systemic symptomatology (eg, body aches, malaise, nausea) onset within 24 hours following administration of IP on ≥3 separate occasions.

To determine whether this dose group stopping rule has been met, the relevant data will be reviewed by the PSRC. The treatment assignment of one or more subjects may be unblinded at the request of the PSRC, as described in Section 3.4.1.2. Following this review, the PSRC will decide if the dose group and other ongoing higher dose groups will:

- Resume unchanged or
- Resume with modifications to the protocol or
- Be terminated.

The Sponsor is responsible for notifying the relevant regulatory authorities and the Investigator is responsible for promptly notifying the relevant IRB of the decision.

4.5.6. Study Stopping Criteria

IP administration will be halted for all subjects if any of the following stopping criteria are met:

a. A subject experiences a Grade 4, life-threatening treatment-emergent AE or death that is considered probably or definitely related to IP by the Investigator
b. Two or more subjects in a dose group experience 1 or more moderate or severe pulmonary exacerbations during the 5-week treatment period in Part B or through Day 11 (1 week post-5th dose) in Part D
c. Two or more subjects in a dose group experience an absolute decrease in predicted FEV1 of at least 25 % compared to the baseline value (defined as the average of the Day -1 and Day 1 pre-dose values) during the 5-week treatment period in Part B or through Day 11 (1 week post-5th dose) in Part D that cannot be explained, in the opinion of the Investigator, by the underlying disease of CF and that is confirmed on 2 separate occasions at least 3 days apart
d. Two or more subjects in the study experience a suspected serious allergic/hypersensitivity reaction, including but not limited to anaphylaxis, generalized rash or bronchospasm likely to be related to drug treatment
e. Two or more subjects in a dose group experience a deterioration in liver function, as detailed below:
    i. Elevation of ALT or AST to >5x ULN in a subject regardless of baseline value
    ii. Elevation of ALT or AST to >3x ULN in a subject with a normal baseline or elevation of >3x ULN from the subject's actual baseline if not normal, with the

appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

iii. Elevation of ALT or AST to >3x ULN in a subject with a normal baseline or elevation of >3x ULN from the subject's actual baseline if not normal, and total bilirubin >2x ULN or INR >1.5.

To determine whether these stopping rules have been met, all available data relating to the safety of the IP will be reviewed by the PSRC. The treatment assignment of one or more subjects may be unblinded at the request of the PSRC, as described in Section 3.4.1.2. Following this review, the PSRC will decide if the study will:

- Resume unchanged or
- Resume with modifications to the protocol or
- Be terminated.

The Sponsor is responsible for notifying the relevant regulatory authorities and the Investigator is responsible for promptly notifying the relevant IRB of the decision.

5. PRIOR AND CONCOMITANT TREATMENT AND PROCEDURES

5.1. Prior and Concomitant Medications and Therapies

Information on all prior and concomitant medications administered from 30 days before the date of informed consent signing through the final study visit on Day 337 (±3 days) in Part A, Day 365 (±3 days) in Part B, or Day 341 (±3 days) in Part D of the study must be recorded on the appropriate CRF page. This includes the subject's routine and non-routine CF medications, other medications, and herbal and homeopathic preparations.

All therapies being taken by the patients on entry to the study or at any time during the study are regarded as concomitant therapies and will be documented on the appropriate pages of the CRF. These include but are not limited to airway clearance techniques.

5.1.1. Permitted Medications and Therapies

Subjects should remain on a stable medication regimen for CF from at least 28 days prior to the screening visit through the final study visit on Day 337 (±3 days) in Part A, Day 365 (±3 days) in Parts B, or Day 341 (±3 days) in Part D of the study. These may include but are not limited to routine inhaled therapies directed at airway clearance and management of respiratory infections, such as bronchodilators, rhDNase (PULMOZYME), hypertonic saline, antibiotics, and steroids; and other routine CF-related therapies such as systemic antibiotics, pancreatic enzymes, multivitamins, and diabetes and liver medications. The timing of subject participation and routine treatment with cycled inhaled antibiotics will be left up to the discretion of the Investigator.

Hormone replacement therapies, thyroid hormone replacement therapy, and non-steroidal inflammatory drugs are also permitted.

Any other medications which are considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator. For example, for subjects experiencing a pulmonary exacerbation, therapeutic interventions may include oral or intravenous administration of antibiotics, oral or parenteral nutritional support, frequent airway clearance techniques, augmented bronchodilator therapy, and corticosteroids.

Other specific medications permitted during the study are listed below:

- Hormonal contraceptives for females of childbearing potential administered according to the package insert (see Section 4.4.1).
- Lumacaftor/ivacaftor combination drug (ORKAMBI) or tezacaftor/ivacaftor combination drug (SYMDEKO). For Part D only: elexacaftor/tezacaftor/ivacaftor triple combination (TRIKAFTA). To be eligible, subjects must have been on stable treatment with these medications for at least 28 days prior to the screening visit and should remain on it for the duration of the study.

Subjects should remain on their routine CF therapies, which include but are not limited to airway clearance techniques.

5.1.1.1. Modifications of Subject's Routine Pulmonary Medications and Therapies

If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting beta-agonist or anticholinergic bronchodilator (eg, beta-agonist medication such as albuterol or anticholinergic agent such as ipratropium bromide). These medications should be withheld for at least 4 hours before spirometry testing (Section 7.5.2.12).

On the days of IP dosing, the administration of IP should optimally occur within 2-3 hours after subjects have completed their routine pulmonary therapies (airway clearance and pulmonary medications) for the day. For subjects whose routine airway clearance therapies do not include an inhaled short-acting beta-agonist (or it is not given within the 2 to 3 hour window prior to IP administration), albuterol (2 to 4 puffs) will be administered via metered-dose inhaler approximately 20 minutes before nebulization with IP to minimize any bronchoconstrictive effects. Note that administration of short-acting beta-agonist via nebulization is also permitted at the discretion of the Investigator.

5.1.2. Prohibited Medications

Specific medications not permitted during the study are listed below:

- Ivacaftor monotherapy (KALYDECO)
- Parts A and B only: Triple-combination therapy (TRIKAFTA)

Starting on or switching to TRIKAFTA is acceptable during the follow-up period; however, subjects should not start/switch until at least 2 months after their last dose of study drug so as not to confound the interpretation of the primary and secondary endpoints.

5.2. Concomitant Surgical Procedures

Surgical procedures (eg, ventral hernia repair, tooth extraction, sinus surgery) that occur from the date of informed consent signing through the final study visit must be recorded on the Concomitant Surgical Procedure CRF page. The date(s) of the procedure and the indication for the procedure will be documented. The indication must have a corresponding entry on the Medical History page (for pre-existing conditions) or Adverse Event page (for new or worsened pre-existing conditions), unless the surgical procedure was prophylactic in nature (eg, PICC line placement for CF cleanout).

For any unplanned hospitalization or prolongation of hospitalization, the procedures for safety reporting should be followed (see Section 8).

6. INVESTIGATIONAL PRODUCT

See the Pharmacy Manual for detailed instructions on the preparation of the IP.

Information on the preparation of study product is provided in Section 6.2.2. Labeling and packaging descriptions are provided in Section 6.3.1, and storage conditions are described in Section 6.3.2.

6.1. Identity of Investigational Product

6.1.1. MRT5005

MRT5005 is a lipid nanoparticle suspension consisting of [redacted] mRNA ([redacted] mRNA), the active drug substance, formulated with the [redacted] lipids, [redacted]. MRT5005 is dosed based on its content of [redacted] mRNA.

MRT5005 will be supplied as a sterile suspension in single-use vials. Each vial contains approximately 3.2 mL of MRT5005 at a concentration of 0.6 mg/mL of [redacted] mRNA. An InnoSpire Go nebulizer will be used to administer MRT5005 to the lungs by nebulization. MRT5005 is dosed based on its content of [redacted] mRNA.

Refer to the MRT5005 Investigator's Brochure for further information about the drug product.

6.1.2. Placebo Comparator

Sterile normal saline solution (Sodium Chloride Inhalation Solution, USP 0.9%) will be used as the placebo comparator.

6.1.3. Blinding the Treatment Assignment

This study will be conducted as a randomized, double-blinded, placebo-controlled trial. The blinding of the study will be maintained as described below.

The Investigators and all study staff involved in the evaluation of subject eligibility, administration of IP, and assessment of study outcomes will be blinded to treatment assignment (MRT5005 vs. placebo within each dose group). All subjects and their families, as well as Sponsor personnel in direct contact with the study center, will also be blinded. The blinded Investigator and study staff must not be allowed to know the IP assigned to any study subject and must not be allowed to see the randomization code; IP, its containers or its preparation; or treatment records until planned interim analyses are completed, as specified in Section 6.2.3. In addition, study staff who will be administering IP (and monitoring the subject for any signs or symptoms of respiratory distress) will be instructed not to open the nontransparent medication cup of the InnoSpire Go to visualize the study drug as MRT5005 will appear different than the normal saline placebo (see below). As such, all relevant individuals will be blinded to treatment assignment, thus maintaining the double-blinded conduct of the study.

As the MRT5005 suspension and normal saline placebo will appear different (normal saline will also be supplied in its commercial presentation and stored at a different temperature), designated unblinded members of the study staff and/or pharmacy will be responsible for preparing and dispensing IP into the nebulizers. The unblinded members of the study staff and/or pharmacy will also be responsible for randomizing subjects once their eligibility has been confirmed. The unblinded members of the study staff and pharmacy will be fully trained in their study-related responsibilities. They will not participate in any other part of the study and will maintain the subject treatment assignments in strict confidence. Their roles will be documented on the study center's delegation of authority log.

Sponsor designated unblinded monitors will be permitted access to monitor the IP preparation, dispensing, and accountability records as well as randomization codes during the study.

Circumstances in which treatment assignments may be broken are presented in Section 6.2.3.

6.2. Administration of IP

6.2.1. Allocation of Subjects to Treatment

Within each dosing group in Parts A, B and D of the study, subjects will be randomly assigned to receive either MRT5005 or placebo in a 3:1 ratio. As stated in Section 6.1.3, a designated unblinded member of the study staff or pharmacist will be responsible for randomizing subjects once their eligibility has been confirmed. The randomization will be performed centrally across the multiple sites; the designated unblinded member of the study staff or pharmacist will retrieve the subject's treatment assignment using an interactive web response (IWR) system. Treatment assignments will be held in strict confidence by the unblinded study staff member or pharmacist. If a treatment assignment has been allocated incorrectly, the study monitor must be notified as soon as the error is discovered.

As defined in Section 3.2, a subject is considered enrolled into the study when he or she has been randomized.

Information on unblinding procedures is provided in Section 6.2.3.

6.2.2. Preparation of IP

Designated unblinded members of the study staff and/or pharmacy will be responsible for preparing and dispensing the IP for administration.

MRT5005 will be supplied as a sterile suspension in single-use vials. Each vial contains approximately 3.2 mL of MRT5005 at a concentration of 0.6 mg/mL of [redacted] mRNA. Vials of MRT5005 should be stored frozen as described in Section 6.3.2. Prior to administration, the appropriate number of vials to deliver the dose of MRT5005 should be thawed completely at room temperature (typically requires 40 minutes). The MRT5005 suspension should be brought to room temperature prior to dispensing into the nebulizers.

MRT5005 is dosed based on its content of [redacted] mRNA, the active drug substance. An InnoSpire Go nebulizer will be used to administer MRT5005 by nebulization at a flow rate of approximately 0.3 mL/minute. MRT5005 will be administered to subjects at the following 5 dose levels: 4, 8, 12, 16, 20, and 24 mg of [redacted] mRNA (nominal dose levels). Table 11 shows the volume of MRT5005 suspension to be nebulized and approximate nebulization time for each of the 5 dose levels of MRT5005 (time does not include the scheduled rest periods between nebulizer changes; see Dosing of IP below). The nebulization times are only targets and will vary; as such, these variations should not be reported as protocol deviations.

The medication cup of the InnoSpire Go nebulizer holds a maximum of 8 mL of solution (see instruction manual for InnoSpire Go nebulizer in Appendix 3). As nebulizers will not be refilled during nebulization, multiple nebulizers, as shown in Table 11, will be used to deliver the specified volume for each of the dose levels of MRT5005. The MRT5005 suspension will be divided equally among the nebulizers.

Table 11: Dosing of MRT5005 - Volumes and Nebulization Times

	Dose of MRT5005 (mg)[a]					
	4	**8**	**12**	**16**	**20**	**24**
Total Nebulization Volume (mL)[b]	7	14	21	28	35	42
Nebulization Time (minutes)[c]	22	44	66	89	110	133
No. of Nebulizers[d]	1	2	3	4	5	6

[a] Nominal dose of [redacted] mRNA.

[b] Includes an additional 0.3 mL per each nebulizer to account for the expected residual volume after nebulization. Based on the measurement accuracy of a 10 mL syringe, the volume per nebulizer has been rounded to the nearest 0.2 mL. The total nebulization volume is based on the rounded volume per nebulizer and the number of nebulizers.

[c] Approximate nebulization time is based on a flow rate of 0.3 mL/minute for the InnoSpire Go nebulizer. This represents actual nebulization time and does not include the rest periods between nebulizer changes.

[d] The medication cup of the InnoSpire Go nebulizer holds a maximum of 8 mL of solution. As nebulizers will not be refilled during nebulization, multiple nebulizers, as shown in the table, will be used to deliver the specified volume for each of the dose levels of MRT5005. The MRT5005 suspension will be divided equally among the nebulizers.

Sterile normal saline (Sodium Chloride Inhalation Solution, USP 0.9%) will be used as placebo. To maintain the blind of the study, the volume and nebulization time of placebo, and number of nebulizers used to deliver placebo will match that of the MRT5005 dosing group. Normal saline should be stored (see Section 6.3.2) and administered at room temperature.

For the purposes of this study, the mouthpiece of the nebulizer, which includes the medication cup and filter attachment with its filter, will be considered single-use and will not reused for another administration. Nebulizer handles will not be reused for single dosing of subjects in Part A. However, nebulizer handles will be reused for multiple dosing in Parts B and D. In this case, nebulizer handles will be assigned to and used by only one subject.

6.2.2.1. Dosing of IP

The administration of IP will be performed by a blinded, qualified member of the study staff. For scheduling of IP administration with respect to the subjects' routine pulmonary medications and therapies, refer to Section 5.1.1.1.

For administration of the IP, the subject should be seated comfortably in a chair and the nebulizer should be held in an upright position; the arm holding the nebulizer may be supported according to the subject's preference (eg, resting the elbow on the arm of a phlebotomy chair). The subject will be instructed to place the mouthpiece of the nebulizer between their teeth, with their lips firmly sealed around the mouthpiece, and to breathe through their mouth at their normal rate and tidal volume until the aerosol formation completely stops (see instruction manual for InnoSpire Go micropump nebulizer in Appendix 3). The subject should turn off the nebulizer when taking the mouthpiece out of their mouth (eg, to talk) to avoid loss of IP and to minimize secondary exposure (see below). As described above, multiple nebulizers may be used to deliver IP (Table 11); to reduce the burden of administration, the subject will be offered a 15 to 20-minute rest period before changing to the next nebulizer (if applicable; this interval may be extended if needed for subject tolerability). For example, subjects receiving the 16 mg dose level may have rest periods after the first, second, and third nebulizers for a total of 3 rest periods during the nebulization.

During nebulization of IP, the subject will be monitored closely for any signs or symptoms of respiratory distress (eg, dyspnea, wheezing, bronchospasm). In Part A and Part B, blood pressure, pulse rate, and oxygen saturation measured by pulse oximetry will be continuously monitored during nebulization (except during rest periods) and will be recorded at the end of the nebulization with each of the multiple nebulizers used to deliver the total volume of IP (eg, for the 16 mg dose, values will be recorded at the end of the nebulization with each of the 4 nebulizers used to deliver the 28 mL of total volume); the final recording will count as the Hour 0 time point. Blood pressure, pulse rate, and/or oxygen saturation may be recorded more frequently, if clinically indicated. Body temperature will not be monitored during the dosing period.

6.2.2.2. Secondary Exposure to Study Staff

To mitigate any secondary exposure of study staff to MRT5005 as well as any potential environmental exposure, the exhalation port of the InnoSpire Go will be fitted with a filter. The exhalation port is the primary source of secondary exposure during nebulization; the filter will minimize the amount of IP that could be inhaled by study staff. To further mitigate any potential secondary exposure, as described above, the subject should turn off the nebulizer when taking the mouthpiece out of their mouth during nebulization (eg, to talk). As an added precaution, study staff should wear gloves, a gown, eyewear, and a disposable particulate filtering facepiece respirator (N95 Respirator or equivalent based on institutional policy) during administration of IP. Respirators should be discarded after each use.

6.2.3. Unblinding Treatment Assignments

A description of the blinding procedures is provided in Section 6.1.3.

The treatment assignments for subjects will be kept strictly confidential, accessible only to authorized persons (Section 6.1.3), until the time of unblinding.

The blind will be maintained in the 8, 16, and 24 mg single dose groups in Part A until 1 month after the last dose (Day 29) of the last subject in the 24 mg dose group. The blind will be maintained in the 20 mg single dose group in Part A, as well as the 8, 16, and 12 mg multiple dose groups in Part B until the 1-month timepoint after the last dose (Day 57) of the last subject dosed in the 12 mg dose group. For the 20 mg multiple dose group in Part B (if applicable), the blind will be maintained until the last subject in this group has reached the 1-month timepoint after the last dose day (Day 57). For Part D, the blind will be maintained until the 1-month timepoint after the last dose (Day 32) of the last subject in Part D. Data collection for each subject will continue until 12 months after their last dose.

The treatment assignments should not normally be broken during the study, but may be broken in the following circumstances:

- In an emergency situation where knowledge of the treatment assignment would be necessary for medical management of the subject. Prior to emergency unblinding, and if the situation allows it, the Investigator should first contact the Medical Monitor. If the treatment assignment is broken for an individual subject, the date and time of code break as well as the reason for unblinding must recorded on the CRF.

- In circumstances where unblinding the treatment assignment for an individual subject would be necessary for the assessment of safety. Such unblinding would occur on a case-by-case basis at the request of the PSRC (Section 3.4.1). For example, if IP administration is halted based on the stopping criteria of the study (Section 4.5.6), the safety review may necessitate unblinding of a subject's treatment assignment.

- To ensure subject safety, the PSRC may request unblinding the treatment assignment(s) for an individual subject or for the entire dose group in Parts A or B of the study to help clarify decisions to dose escalate, to repeat a dose group, or to initiate Part B of the study (Sections 3.4.1 and 3.4.2).

- If a reportable safety event occurs in a subject receiving MRT5005, then the subject's treatment assignment will be unblinded and an unblinded MedWatch form and Dear Doctor Letter will be provided to sites and IRBs by the Rho clinical team.

Subjects participating in the study will be informed of their treatment assignment after the interim analysis of the part of the study in which the subject participated is completed.

6.3. Labeling, Packaging, Storage, and Handling

6.3.1. Labeling and Packaging

The Sponsor or designee will provide MRT5005 and placebo for this study. These will be packaged in the labeled containers as described below. Changes to Sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the Sponsor.

6.3.1.1. MRT5005

MRT5005 will be supplied to clinical sites in single-use vials, which will be packaged in cartons containing multiple vials. The vials and cartons will be labeled with a minimum of the protocol number, dosage form including IP name, medication identification number (Lot#), dosing instructions, storage conditions, the statements “CAUTION: New Drug - Limited by Federal (United States) Law to Investigational Use” and the Sponsor's name and address.

6.3.1.2. Placebo Comparator

Commercially available single-use, sterile, normal saline solution (Sodium Chloride Inhalation Solution, USP 0.9%) will be used as placebo in the study. The normal saline solution will be supplied in their commercial vials, which will be over-labeled with an IP label. The placebo vials will be packaged in cartons containing multiple vials; the carton will also be labeled with an IP label.

6.3.2. Storage of IP

- MRT5005 vials should be stored frozen at -80°C ± 5°C (-112°F ± 9°F) in an appropriate freezer until the day of use.

- Normal saline solution (placebo comparator) should be stored at controlled room temperature from 15°C to 30°C (59°F to 86°F).

The Investigator has overall responsibility for ensuring that IP (MRT5005 and placebo) is stored in a secure, limited-access location. Responsibility may be delegated to the pharmacy, but this delegation must be documented. IP should only be prepared by the designated unblinded pharmacist or qualified person, who will enter the unique subject identifier on the IP labels (MRT5005 and placebo vial labels).

MRT5005 and placebo must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that IP is maintained within an established temperature range. The Investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The Sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The Sponsor will determine the ultimate impact of excursions on IP and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the Sponsor.

The Sponsor should be notified immediately if there are any changes to the storage area of IP that could affect the integrity of the product(s), eg, fumigation of a storage room.

The Sponsor designated unblinded monitors will be permitted access to monitor the IP storage area during the study.

6.4. Drug Accountability

Investigators will be provided with sufficient amounts of the IP to carry out this protocol for the agreed number of subjects. The Investigator or designee will acknowledge receipt of IP, documenting shipment content and condition. Accurate records of all IP dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The Investigator has overall responsibility for administering IP. However, to maintain the blind, this task will be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the Investigator. This delegation must be documented in the applicable study delegation of authority form.

The Investigator or his/her designee (as documented by the Investigator in the applicable study delegation of authority form) will administer the IP only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the IP carrying his/her treatment assignment. All administered medication will be documented on the CRFs and/or other IP record.

No IP stock or returned inventory from a Translate Bio-Sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the Sponsor. If such transfer is authorized by the Sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The Sponsor designated unblinded monitors will be permitted access to monitor the IP supplies storage, preparation, dispensing, and accountability records as well as randomization codes during the study.

With the written agreement of the Sponsor, at the end of the study all unused stock and empty/used IP packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how, must be obtained with copies provided to the Sponsor. Destruction of IP must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile IPs delivered with those used, destroyed, or returned. All IPs must be accounted for and all discrepancies investigated and documented to the Sponsor’s satisfaction.

6.5. Subject Compliance

IP is administered under controlled conditions by the Investigator’s designee; therefore, full subject compliance with study treatment is anticipated in this study.

The designated person will record details on the drug accountability log(s) and/or source documents. In addition, details of the dosing time (time and date) will be captured in the appropriate CRF.

7. STUDY PROCEDURES

7.1. Part A Study Schedule

Details regarding the procedures and tests to be performed during each study period and time point for Part A are provided in the Schedule of Procedures in Table 1, Table 2, and Table 3.

Part A of this study consists of 3 periods: a screening period, a treatment period, and a follow-up period (see Figure 1). The duration of the screening period is up to 27 days (Day -28 through Day -2); the duration of the treatment period is 3 days (Day -1 to Day 2); and the duration of the follow-up period is up to 327 days (Day 3 through Day 337 [±3 days]). During the treatment period, Part A subjects will be admitted to the study center on Day -1 and will be confined to the study center (inpatient) until discharged on Day 2 of the study. During the follow-up period, subjects will perform all clinic visits as outpatients.

All AEs and SAEs, regardless of relationship, will be collected from the time the subject signs the informed consent until the final study visit on Day 337 (±3 days). Information on all prior and concomitant medications administered from 30 days before the date of informed consent signing through the final study visit on Day 337 (±3 days) must be recorded on the appropriate CRF page.

Time Windows for the Schedule of Procedures:

No obligatory time windows are set for the study time points in order to allow for flexibility in the conduct of the study. The time windows provided in Table 1, Table 2, and Table 3 are suggested guidelines to be followed during the conduct of Part A. As these guidelines are only suggestions, they will not result in protocol deviations.

Priority Order for Performing Procedures and Tests:

The following “priority order” will be in effect when more than 1 procedure or test is required at a particular time point.

- Review of AEs, concomitant medications, and concomitant surgical procedures
- Vital signs, pulse oximetry
- Physical examination
- Spirometry
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis, CRP)
- ECG
- Chest x-ray

- Other procedures with lower priorities (weight measurement; blood sampling for [redacted] mRNA and [redacted] assays; and blood sampling for immune response assays)

On the days when serum or urine pregnancy testing is being performed, scheduled or unscheduled, this test has priority.

7.1.1. Screening Period: Day -28 to Day -2

See Table 1 for the Schedule of Procedures for the screening period of Part A.

Written, signed, and dated informed consent (specific for Part A) must be obtained by the Investigator or a designee from the subject prior to the performance of any study-related procedures or tests. A copy of the informed consent form must be given to the subject for their records.

At the initial screening visit, informed consent will be obtained from the subject. A unique subject identification number will then be assigned, which will serve as the subject's identifier throughout the study and in the CRF. Inclusion and exclusion criteria will be reviewed to assess the subject's eligibility; and demographic information, and medical and medication history will be collected. Collection of AEs, concomitant medications, and concomitant surgical procedures will begin from the time the subject signs the informed consent.

All screening procedures and tests must be completed during the screening period and prior to returning to the study center on Day -1. Multiple visits may be necessary for the subject to complete all of the required screening procedures and tests. If a screening test is considered to be invalid upon subsequent review (eg, spirometry testing) or not representative of the subject's usual baseline status, it may be repeated at the discretion of the Investigator. All screening procedures and tests are to be performed by the Investigator or a qualified designee.

The baseline chest x-ray may be performed at any time from Day -14 to Day -2 during the screening period. If feasible for the subject, all spirometry testing for the study should be performed "pre-bronchodilator" for those subjects receiving treatment with a short-acting beta-agonist or anticholinergic bronchodilator, as described in Section 7.5.2.12.

Subject eligibility for the study will be determined based on the procedures and tests performed during the screening period. (As described in Section 7.1.2, subsequent testing performed on Day -1 and pre-dose on Day 1 will be used to confirm eligibility; these results will only be exclusionary for subjects if there is a clinically significant or relevant change in a result, as determined by the Investigator.)

7.1.1.1. Screening Failure

A screen failure is a subject who has given informed consent and failed to meet the inclusion criteria or met at least 1 of the exclusion criteria and has not been enrolled into the study (ie, not randomized).

For the purposes of data collection, consented subjects who were fully eligible for the study but were otherwise not enrolled (eg, example alternates/reserve subjects) will also be considered screen failures.

7.1.1.2. Rescreening of Subjects

Based on Investigator discretion and Sponsor approval, subjects who initially failed to meet the inclusion/exclusion criteria may be rescreened at a later time if their eligibility status has changed (eg, resolution of a transient event such as an acute upper respiratory infection or pulmonary exacerbation).

For subjects who initially met all inclusion/exclusion criteria, but due to scheduling conflicts or study delays were unable to enroll into the study within the screening period window, based on the Investigator's discretion and Sponsor's approval, the subject may be allowed to enroll by extending the window for the screening period or may choose to be rescreened at a later time.

Enrolled subjects who discontinue treatment after one dose of study drug for a reason unrelated to safety (eg, interrupted clinical research activities due to coronavirus disease pandemic) may be rescreened at a later time at the discretion of the Sponsor. Such subjects may receive no more than 5 weekly doses of study drug in total.

In all cases of rescreening, a new informed consent form must be signed by the subject. Rescreened subjects who did not enroll in the study will retain the same subject identification number that he/she was assigned at the first screening. Rescreened subjects who previously enrolled in the study will be assigned a new subject identification number.

7.1.2. Treatment Period: Day -1 to Day 2

See Table 1 for the Schedule of Procedures for the treatment period of Part A.

Following screening, eligible subjects will return to the study center on Day -1 of the treatment period. Subjects will be admitted to the study center on Day -1 and will be confined to the study center (inpatient) until discharged on Day 2.

On Day -1, the baseline procedures and tests as described in Table 1 will be performed. The Day -1 results must be reviewed by the Investigator to ensure that subjects continue to be eligible for study enrollment (see Section 7.1.1.1 for definition of screening failure).

Pre-dose assessments on Day 1 include a limited physical examination, measurement of vital signs and oxygen saturation (pulse oximetry), and ECG and spirometry testing. The limited physical examination, vital signs and pulse oximetry must be performed prior to randomization. ECG and spirometry may be performed after randomization, but MUST be performed, and reviewed prior to the dose, to confirm continued eligibility.

Subjects will be randomized to treatment and thereby enrolled in the study after the following 2 conditions have been met:

1. Subject meets all of the inclusion criteria and none of the exclusion criteria during the screening period and Day -1 (as applicable) as specified in the eligibility criteria in Section 4.1 and Section 4.2.

2. Confirmation of eligibility on Day 1. Results from the Day -1 and pre-dose tests on Day 1 (AE, conmeds, pulse oximetry, physical exam, vital signs) do not reveal a new safety issue making the subject ineligible for randomization. A subject is considered enrolled into the study when he or she has been randomized to treatment. Pre-dose tests that may occur after randomization but MUST occur and be reviewed by the PI prior to first dose include spirometry and ECG. If the pre-dose Day 1 ECG or spirometry results reveal a safety issue making it inadvisable to administer the dose to the randomized subject, then the subject will be considered an Early Discontinuation.

If the subject is receiving treatment with an inhaled short-acting bronchodilator as part of their routine pulmonary therapies (see below), pre-dose spirometry testing may be scheduled before the subject's pulmonary therapies so that it can be performed "pre-bronchodilator." Recording of any AEs and concomitant medications should continue at this time. The procedures and tests performed on Day -1 and Day 1will be used to confirm eligibility. A clinically significant or relevant change in a result during pre-dose assessments, as determined by the Investigator, may be exclusionary (new or worsening adverse event or worsened pulse oximetry reading).

Prior to IP administration, subjects should undergo their routine pulmonary therapies (airway clearance and pulmonary medications) at the study center. These may include but are not limited to chest physiotherapy, and treatment with inhaled bronchodilators, hypertonic saline, antibiotics, and steroids (Section 5.1.1). The administration of IP should optimally occur within 2 to 3 hours after subjects have completed their pulmonary therapies for the day. For subjects whose routine pulmonary medications do not include an inhaled short-acting beta-agonist (or it is not given within the 2 to 3 hour window prior to IP administration), albuterol (2 to 4 puffs) will be administered via metered-dose inhaler approximately 20 minutes before treatment with IP to minimize any potential bronchoconstrictive effects (Section 5.1.1.1). Note that administration of short-acting beta-agonist via nebulization is also permitted at the discretion of the Investigator.

Following confirmation of eligibility, subjects will be randomized to receive a single dose of either MRT5005 or placebo (subjects who are randomized are considered enrolled into the study). The administration of IP will be performed by a blinded, qualified member of the study staff. IP will be administered by the respiratory route using an InnoSpire Go nebulizer. Depending on the dose level, nebulization times will range from approximately 44 to 133 minutes. Blood pressure, pulse rate, and oxygen saturation measured by pulse oximetry will be monitored continuously during nebulization. The subject will also be monitoring closely for any signs or symptoms of respiratory distress (eg, dyspnea, wheezing, bronchospasm). See Section 6.2.2 for details on the preparation and dosing of IP, which includes minimizing secondary exposure to study staff during nebulization of IP.

Following IP administration, the procedures and tests (Table 1) will be performed at the specified time points on Days 1 and 2. If there are any ongoing AEs or safety concerns of clinical significance at the 8-hour time point on Day 1 (eg, decreased oxygen saturation or airway symptoms), appropriate monitoring should continue until the AE or safety concern has resolved.

Subjects can be discharged when all of the Day 2 assessments have been completed and when subjects have been deemed clinically stable by the Investigator with no ongoing AEs or safety concerns of clinical significance. Discharged subjects should be housed overnight close to the study center until the clinic visit on the following day (Day 3). If a subject is experiencing an ongoing AE or there is a safety concern on Day 2, based on the judgment of the Investigator, the subject can remain in the study center overnight or can be hospitalized for continued monitoring until the clinic visit on the following day (Day 3). The subject should remain in the study center or hospital until the AE or safety concern has resolved and the subject is sufficiently stable to be discharged.

At discharge, all subjects will be instructed to return to the study center for their scheduled clinic visit on Day 3 (or for their next scheduled clinic visit, if not Day 3). Subjects will be instructed to return to the study center or call the study staff immediately if they are experiencing any symptoms of concern, either new or worsening, or were hospitalized or required a visit to the emergency department for any reason.

7.1.3. Follow-up Period: Day 3 to Day 337

See Table 2 and Table 3 for the Schedule of Procedures for the follow-up period of Part A.

Safety will be monitored for 12 months (48 weeks) after administration of IP. The safety follow-up period continues through the final study visit on Day 337 (±3 days).

Subjects will return for outpatient clinic visits on Days 3, 8, 15, 29, 57, 85, 169, 253, and 337 to perform the follow-up procedures and tests scheduled for this period, as described in Table 2 and Table 3. Telephone contact with the subject will occur on Days 5, 11, 18, 22, 43, 71, 113, 141, 197, 225, 281, and 309 to query the subject about the occurrence of any AEs/SAEs, any changes in concomitant medications or concomitant surgical procedures.

During the clinic visits and telephone contacts, subjects will be reminded to return to the study center or call the study staff immediately if they are experiencing any symptoms of concern, either new or worsening, or were hospitalized or required a visit to the emergency department for any reason.

If a subject is experiencing respiratory distress or respiratory symptoms, based on the Investigator's judgment, unscheduled spirometry testing may be performed when the subject is stable. In addition, at the discretion of the Investigator, an unscheduled chest x-ray may be performed at any time during the follow-up period if the subject is experiencing respiratory symptoms that warrant it.

In addition to the time points specified in the schedule of assessments, immunogenicity testing will also be performed when immunogenicity is suspected, such as allergy/hypersensitivity events or unexplained bronchospasm.

Study completion for each subject is defined as the last study assessment for that subject on Day 337 (±3 days). All ongoing AEs on Day 337 must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal). Closure

indicates that an outcome is reached, stabilization achieved (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

7.2. Part B Study Schedule

Details regarding the procedures and tests to be performed during each study period and time point for Part B are provided in the Schedule of Procedures in Table 4, Table 5, Table 6, and Table 7.

Similar to Part A of this study, Part B will consist of a screening period, a treatment period, and a follow-up period (see Figure 1). The duration of the screening period is up to 27 days (Day -28 through Day -2); the duration of the treatment period is 36 days (Day -1 to Day 35); and the duration of the follow-up period is up to 332 days (Day 36 through Day 365 [±3 days]). No confinement (inpatient) will be required of subjects in Part B; subjects will perform all clinic visits as outpatients.

All AEs and SAEs, regardless of relationship, will be collected from the time of informed consent signing until the final study visit on Day 365 (±3 days). Information on all prior and concomitant medications administered from 30 days before the date of informed consent signing through the final study visit on Day 365 (±3 days) must be recorded on the appropriate CRF page.

Time Windows for the Schedule of Procedures:

No obligatory time windows are set for the study time points in order to allow for flexibility in the conduct of the study. The time windows provided in Table 4, Table 5, Table 6, and Table 7 are suggested guidelines to be followed during the conduct of Part B. As these guidelines are only suggestions, they will not result in protocol deviations.

Priority Order for Performing Procedures and Tests:

The following priority order will be in effect when more than 1 procedure or test is required at a particular time point.

- AE, concomitant medication, and concomitant surgical procedure reporting
- Vital signs, pulse oximetry
- Physical examination
- Spirometry
- Clinical laboratory tests (serum chemistry, hematology, coagulation, urinalysis, CRP)
- ECG

- Chest x-ray
- Other procedures with lower priorities (weight measurement; blood sampling for [redacted] mRNA and [redacted] assays, and for immune response assays)

On the days when serum or urine pregnancy testing is being performed, scheduled or unscheduled, this test has priority.

7.2.1. Screening Period: Day -28 to Day -2

See Table 4 for the Schedule of Procedures for the screening period of Part B.

Written, signed, and dated informed consent must be obtained by the Investigator or a designee from the subject prior to the performance of any study-related procedures or tests. A copy of the signed informed consent form must be given to the subject for their records.

At the initial screening visit, informed consent will be obtained from the subject. A unique subject identification number will then be assigned, which will serve as the subject's identifier throughout the study and in the CRF. Inclusion and exclusion criteria will be reviewed to assess the subject's eligibility; and demographic information, and medical and medication history will be collected. Collection of AEs and concomitant medications will begin from the time the subject signs the informed consent.

Subjects participating in Part B of the study will perform all of the same procedures and tests during the screening period as in Part A. All screening procedures and tests must be completed during the screening period and prior to returning to the study center on Day -1. Multiple visits during the screening period may be necessary for the subject to complete all of the required screening procedures and tests. If a screening test is considered to be invalid upon subsequent review (eg, spirometry testing) or not representative of the subject's usual baseline status, it may be repeated at the discretion of the Investigator. All screening procedures and tests are to be performed by the Investigator or a qualified designee.

The baseline chest x-ray may be performed at any time from Day -14 to Day -2 during the screening period. If feasible for the subject, all spirometry testing for the study should be performed "pre-bronchodilator" for those subjects receiving treatment with a short-acting beta-agonist or anticholinergic bronchodilator, as described in Section 7.5.2.12.

Subject eligibility for the study will be determined based on the procedures and tests performed during the screening period. As described in Section 7.1.2, subsequent testing performed on Day -1 and Day 1 will be used to confirm eligibility. A clinically significant or relevant change in a result during pre-dose assessments, as determined by the Investigator, may be exclusionary (eg, new or worsening adverse event or worsened pulse oximetry reading).

7.2.1.1. Screening Failure

The definition of a subject who is a screen failure, as described in Section 7.1.1.1 for Part A, also applies to Part B.

7.2.1.2. Rescreening of Subjects

Rescreening of subjects, as described in Section 7.1.1.2 for Part A, also applies to Part B.

7.2.2. Treatment Period: Day -1 to Day 33

See Table 4 and Table 7 for the Schedule of Procedures for the treatment period of Part B.

Following screening, eligible subjects will return to the study center on Day -1 and will perform the baseline procedures and tests, as described in Table 4. The Day -1 results must be reviewed by the Investigator to ensure that subjects continue to be eligible for study enrollment (see Section 7.1.1.1 for definition of screening failure).

Subjects will return to the study center the following day (Day 1). Pre-dose assessments on Day 1 should be performed immediately prior to IP administration; these assessments include a limited physical examination, measurement of vital signs and oxygen saturation (pulse oximetry), and spirometry testing. If the subject is receiving treatment with an inhaled short-acting bronchodilator as part of their routine pulmonary therapies (see below), pre-dose spirometry testing may be scheduled before the subject's pulmonary therapies (if the subject's schedule permits) so that it can be performed "pre-bronchodilator." Alternatively, the subject may choose to delay the bronchodilator treatment until after the pre-dose spirometry testing is performed and receive the treatment just prior to the administration of IP, as described below. Recording of any AEs and concomitant medications should continue at this time. The procedures and tests performed on Day -1 and pre-dose on Day 1 will be used to confirm eligibility; these results will only be exclusionary for subjects if there is a clinically significant or relevant change in a result, as determined by the Investigator (eg, positive pregnancy test).

Prior to IP administration, subjects should undergo their routine pulmonary therapies (airway clearance and pulmonary medications). These may be administered either at home or at the study center and may include but are not limited to chest physiotherapy, and treatment with inhaled bronchodilators, hypertonic saline, antibiotics, and steroids (Section 5.1.1). The administration of IP should optimally occur within 2 to 3 hours after subjects have completed their pulmonary therapies for the day. For subjects whose routine pulmonary medications do not include an inhaled short-acting beta-agonist (or it is not given within the 2 to 3 hour window prior to IP administration), albuterol (2 to 4 puffs) will be administered via metered-dose inhaler approximately 20 minutes before treatment with IP to minimize any potential bronchoconstrictive effects (Section 5.1.1.1). Note that administration of a short-acting beta-agonist via nebulization is also permitted at the discretion of the Investigator

Following confirmation of eligibility, subjects will be randomized to receive the first dose of either MRT5005 or placebo (subjects who are randomized are considered enrolled into the study). The administration of IP will be performed by a blinded, qualified member of the study staff. IP will be administered by the respiratory route using an InnoSpire Go nebulizer. Depending on the dose level, nebulization times will range from approximately 44 to 133 minutes. During nebulization, blood pressure, pulse rate, and oxygen saturation measured by pulse oximetry will be monitored continuously, together with close monitoring of the subject for any signs or symptoms of respiratory distress (eg, dyspnea, wheezing, bronchospasm). See

Section 6.2.2 for details on the preparation and dosing of IP, which includes minimizing secondary exposure to study staff during nebulization of IP.

The second through fifth doses of IP will be administered on Days 8, 15, 22, and 29, respectively. IP dosing should occur on approximately the same day of Weeks 1 through 5 (eg, every Tuesday [the day of the week is defined by the first dose given on Day 1 of Week 1]), but may occur ±1 day of the target day for Weeks 2 through 5 in order to facilitate subject scheduling. The pre-dose assessments will be identical to those performed for the first dose (with some additional pre-dose assessments on Days 8, 15, 22, and 29 as noted in Table 7), and IP should continue to be administered within 2 to 3 hours after subjects have completed their routine pulmonary therapies. In addition, instructions regarding the use of rhDNase (PULMOZYME) and short-acting beta-agonist therapies should continue to be followed for all doses.

On dosing days (Table 7), subjects will remain in the clinic for safety monitoring for at least 6 hours after administration of IP and will be discharged only when deemed clinically stable by the Investigator with no ongoing AEs or safety concerns of clinical significance. Discharged subjects can go home if they live locally (within 1 hour driving distance from the study center) or if not should be housed overnight close to the study center until the clinic visit on the following day. If a subject is experiencing an ongoing AE or there is a safety concern at the 6-hour time point (eg, decreased oxygen saturation by pulse oximetry or airway symptoms), based on the judgment of the Investigator, the subject can remain in the study center overnight or can be hospitalized for continued monitoring until the clinic visit on the following day. The subject should remain in the study center or hospital until the AE or safety concern has resolved and the subject is sufficiently stable to be discharged.

Subjects will be provided a digital thermometer and Body Temperature Recording Log for measuring and recording his/her body temperature after discharge on each dosing day. Subjects will be asked to record his/her body temperature at regular intervals until bedtime and as needed overnight should febrile symptoms (eg, chills, night sweats) awaken the subject from sleep on each dosing day.

At discharge on each dosing day, subjects will be instructed to return to the clinic on the following day (Days 2, 9, 16, 23, and 30). The procedures and tests, as described in Table 4, will be performed at this post-treatment clinic visit. Following these outpatient clinic visits, subjects will be contacted approximately 3 days later by telephone on Days 5, 12, 19, 26, and 33, to query the subject about the occurrence of any AEs/SAEs and any changes in concomitant medications.

If a subject is experiencing respiratory distress or respiratory symptoms, based on the Investigator's judgment, unscheduled spirometry testing may be performed when the subject is stable. In addition, at the discretion of the Investigator, an unscheduled chest x-ray may be performed at any time during the treatment period if the subject is experiencing respiratory symptoms that warrant it.

During the clinic visits and telephone contacts, subjects will be reminded to return to the study center or call the study staff immediately, if they are experiencing any symptoms of concern,

either new or worsening, or were hospitalized or required a visit to the emergency department for any reason.

7.2.3. Follow-up Period: Day 36 to Day 365

See Table 5 and Table 6 for the schedule of procedures for the follow-up period of Part B.

Safety will be monitored for 12 months after administration of the fifth dose of IP in Part B. The safety follow-up period continues through the last study visit on Day 365 (±3 days).

Subjects will return for outpatient clinic visits on Days 36, 43, 57, 71, 85, 113, 197, 281, and 365 to perform the follow-up procedures and tests scheduled for this period. Telephone contact with the subject will occur on Days 39, 46, 50, 64, 78, 99, 141, 169, 225, 253, 309, and 337 to query the subject about the occurrence of any AEs/SAEs and any changes in concomitant medications. Subjects will also be instructed at every clinic visit and telephone contact to return to the study or call the study staff immediately if they are experiencing any symptoms of concern, either new or worsening, or were hospitalized or required a visit to the emergency department for any reason.

If a subject is experiencing respiratory distress or respiratory symptoms, based on the Investigator's judgment, unscheduled spirometry testing may be performed when the subject is stable. In addition, at the discretion of the Investigator, an unscheduled chest x-ray may be performed at any time during the follow-up period if the subject is experiencing respiratory symptoms that warrant it.

Study completion for each subject is defined as the last study assessment for that subject on Day 365 (±3 days). All ongoing AEs on Day 365 must be followed to closure (when the subject's health has returned to his/her baseline status or when all variables have returned to normal). Closure indicates that an outcome is reached, stabilization achieved (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations may be performed so that resolution of event(s) can be documented.

7.3. Part D Study Schedule

Details regarding the procedures and tests to be performed during each study period and time point for Part D are provided in the Schedule of Procedures in Table 8 and Table 9.

Part D will consist of a screening period, a treatment period, and a follow-up period (see Figure 1). The duration of the screening period is up to 28 days (Day -28 through Day -1); the duration of the treatment period is 5 days (Day 1 to Day 5); and the duration of the follow-up period is up to 336 days (Day 6 through Day 341 [±3 days]). No confinement (inpatient) will be required of subjects in Part D; subjects will perform all clinic visits as outpatients.

All AEs and SAEs, regardless of relationship, will be collected from the time of informed consent signing until the final study visit on Day 341 (±3 days). Information on all prior and concomitant medications administered from 30 days before the date of informed consent signing

through the final study visit on Day 341 (±3 days) must be recorded on the appropriate CRF page.

Time Windows for the Schedule of Procedures:

No obligatory time windows are set for the study time points in order to allow for flexibility in the conduct of the study. The time windows provided in Table 8 and Table 9 are suggested guidelines to be followed during the conduct of Part D. As these guidelines are only suggestions, they will not result in protocol deviations if they cannot be adhered to.

Priority Order for Performing Procedures and Tests:

The same priority order as for Part B (Section 7.2) will be in effect when more than 1 procedure or test is required at a particular time point in Part D.

7.3.1. Screening Period: Day -28 to Day -1

See Table 8 for the Schedule of Procedures for the screening period of Part D.

Written, signed, and dated informed consent must be obtained by the Investigator or a designee from the subject prior to the performance of any study-related procedures or tests. A copy of the signed informed consent form must be given to the subject for their records.

At the initial screening visit, informed consent will be obtained from the subject. A unique subject identification number will then be assigned, which will serve as the subject's identifier throughout the study and in the CRF. Inclusion and exclusion criteria will be reviewed to assess the subject's eligibility; and demographic information, and medical and medication history will be collected. Collection of AEs and concomitant medications will begin from the time the subject signs the informed consent.

Subjects participating in Part D of the study will perform all of the same procedures and tests during the screening period as in Parts A and B. All screening procedures and tests must be completed during the screening period and prior to returning to the study center on Day 1. Multiple visits during the screening period may be necessary for the subject to complete all of the required screening procedures and tests. If a screening test is considered to be invalid upon subsequent review (eg, spirometry testing) or not representative of the subject's usual baseline status, it may be repeated at the discretion of the Investigator. All screening procedures and tests are to be performed by the Investigator or a qualified designee.

The baseline chest x-ray may be performed at any time from Day -14 to Day -1 during the screening period. If feasible for the subject, all spirometry testing for the study should be performed "pre-bronchodilator" for those subjects receiving treatment with a short-acting beta-agonist or anticholinergic bronchodilator, as described in Section 7.5.2.12.

Subject eligibility for the study will be determined based on the procedures and tests performed during the screening period. As described in Section 7.1.2, subsequent testing performed on Day 1 will be used to confirm eligibility. A clinically significant or relevant change in a result

during pre-dose assessments, as determined by the Investigator, may be exclusionary (eg, new or worsening adverse event or worsened pulse oximetry reading).

7.3.1.1. Screening Failure

The definition of a subject who is a screen failure, as described in Section 7.1.1.1 for Part A, also applies to Part D.

7.3.1.2. Rescreening of Subjects

Rescreening of subjects, as described in Section 7.1.1.2 for Part A, also applies to Part D.

7.3.2. Treatment Period: Day 1 to Day 5

See Table 8 for the Schedule of Procedures for the treatment period of Part D.

Following screening, eligible subjects will return to the study center on Day 1 and will perform the baseline procedures and tests, as described in Table 8.

Pre-dose assessments on Day 1 should be performed prior to IP administration; these assessments include a pregnancy test (female subjects only), collection of blood for safety labs, limited physical examination, measurement of vital signs and oxygen saturation (pulse oximetry), and spirometry testing. If the subject is receiving treatment with an inhaled short-acting bronchodilator as part of their routine pulmonary therapies (see below), pre-dose spirometry testing may be scheduled before the subject's pulmonary therapies (if the subject's schedule permits) so that it can be performed "pre-bronchodilator." Alternatively, the subject may choose to delay the bronchodilator treatment until after the pre-dose spirometry testing is performed and receive the treatment just prior to the administration of IP, as described below. Recording of any AEs and concomitant medications should continue at this time. The only procedures and tests performed pre-dose on Day 1 that will be used to confirm eligibility are the limited physical exam, vital signs, pregnancy test, and pulse oximetry; these results will only be exclusionary for subjects if there is a clinically significant or relevant change in a result, as determined by the Investigator (eg, positive pregnancy test).

Prior to IP administration, subjects should undergo their routine pulmonary therapies (airway clearance and pulmonary medications). These may be administered either at home or at the study center and may include but are not limited to chest physiotherapy, and treatment with inhaled bronchodilators, hypertonic saline, antibiotics, and steroids (Section 5.1.1). The administration of IP should optimally occur within 2 to 3 hours after subjects have completed their pulmonary therapies for the day. For subjects whose routine pulmonary medications do not include an inhaled short-acting beta-agonist (or it is not given within the 2 to 3 hour window prior to IP administration), albuterol (2 to 4 puffs) will be administered via metered-dose inhaler approximately 20 minutes before treatment with IP to minimize any potential bronchoconstrictive effects (Section 5.1.1). Note that administration of a short-acting beta-agonist via nebulization is also permitted at the discretion of the Investigator

Following confirmation of eligibility, subjects will be randomized to receive the first dose of either MRT5005 or placebo (subjects who are randomized are considered enrolled into the study). The administration of IP will be performed by a blinded, qualified member of the study staff. IP will be administered by the respiratory route using an InnoSpire Go nebulizer. Nebulization time is expected to be approximately 22 minutes or less. See Section 6.2.2 for details on the preparation and dosing of IP, which includes minimizing secondary exposure to study staff during nebulization of IP.

The second through fifth doses of IP will be administered on Days 2, 3, 4, and 5, respectively. Pre-dose assessments will occur on each dosing day (as noted in Table 8) and IP should continue to be administered within 2 to 3 hours after subjects have completed their routine pulmonary therapies.

On each dosing day, subjects will remain in the clinic for safety monitoring for at least 2 hours after administration of IP and will be discharged only when deemed clinically stable by the Investigator with no ongoing AEs or safety concerns of clinical significance. Discharged subjects may go home if they live locally (within 1 hour driving distance from the study center) or if not should be housed overnight close to the study center until the clinic visit on the following day. If a subject is experiencing an ongoing AE or there is a safety concern at the 2-hour time point (eg, decreased oxygen saturation by pulse oximetry or airway symptoms), based on the judgment of the Investigator, the subject should remain in the study center or hospital until the AE or safety concern has resolved and the subject is sufficiently stable to be discharged.

If a subject is experiencing respiratory distress or respiratory symptoms, based on the Investigator's judgment, unscheduled spirometry testing may be performed when the subject is stable. In addition, at the discretion of the Investigator, an unscheduled chest x-ray may be performed at any time during the treatment period if the subject is experiencing respiratory symptoms that warrant it.

Subjects will be provided a digital thermometer and Body Temperature Recording Log for measuring and recording his/her body temperature after discharge on each dosing day. Subjects will be asked to record his/her body temperature at regular intervals until bedtime and as needed overnight should febrile symptoms (eg, chills, night sweats) awaken the subject from sleep.

7.3.3. Follow-up Period: Day 6 to Day 341

See Table 8 and Table 9 for the schedule of procedures for the follow-up period of Part D.

After being discharged after the final dosing day on Day 5, subjects will be contacted approximately 3 days later by telephone on Day 8 to monitor the occurrence of any AEs/SAEs and any changes in concomitant medications. Subjects will return to the clinic on Day 11 for the first outpatient follow-up clinic visit including the procedures and tests, as described in Table 8.

Safety will be monitored for 48 weeks after administration of the fifth dose of IP in Part D. The safety follow-up period continues through the last study visit on Day 341 (±3 days).

Subjects will return for outpatient clinic visits on Days 18, 32, 60, 145, 229, and 341 to perform the follow-up procedures and tests scheduled for this period, as described in Table 9. Telephone contact with the subject will occur on Days 25, 46, 89, 117, 173, 201, 257, 285, and 313 to query the subject about the occurrence of any AEs/SAEs and any changes in concomitant medications. Subjects will also be instructed at every clinic visit and telephone contact to return to the study or call the study staff immediately if they are experiencing any symptoms of concern, either new or worsening, or were hospitalized or required a visit to the emergency department for any reason.

If a subject is experiencing respiratory distress or respiratory symptoms, based on the Investigator's judgment, unscheduled spirometry testing may be performed when the subject is stable. In addition, at the discretion of the Investigator, an unscheduled chest x-ray may be performed at any time during the follow-up period if the subject is experiencing respiratory symptoms that warrant it.

Study completion for each subject is defined as the last study assessment for that subject on Day 341 (±3 days). All ongoing AEs on Day 341 must be followed to closure (when the subject's health has returned to his/her baseline status or when all variables have returned to normal). Closure indicates that an outcome is reached, stabilization achieved (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations may be performed so that resolution of event(s) can be documented.

7.4. Additional Care of Subjects after the Study

No after care is planned for this study.

7.5. Study Evaluations and Procedures

All procedures and tests are to be performed by the Investigator or a qualified designee who has been trained in the protocol. All procedures and tests are to be performed according to the Schedule of Procedures in Table 1 through Table 9.

7.5.1. Demographic and Other Baseline Characteristics

Demographic characteristics (age, sex, and race) will be collected at the initial screening visit and reviewed on Day -1 (Parts A and B only). Weight will be taken at both the screening visit and on Day -1 (Parts A and B only); height will only be taken at the initial screening visit. In Part D, demographic characteristics, weight, and height will only be recorded at the Screening visit. BMI will be calculated based on the subject's weight and height collected at the initial screening visit.

7.5.2. Safety

The name and address of each third party vendor used in this study will be maintained in the Investigator's and Sponsor's files, as appropriate.

Actual safety assessment times will be monitored and recorded. The Sponsor's expectation is that the Investigator will ensure that every effort is made to perform all assessments at the protocol-scheduled time according to the suggested guidelines described in Section 7.1.

The Investigator can use their judgment in performing the following procedures as described in the Schedule of Procedures in Table 1 through Table 9.

- If a subject is experiencing respiratory distress or respiratory symptoms, based on the judgment of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.
- At the Investigator's discretion, a chest x-ray may be performed at any time during the study if the subject is experiencing respiratory symptoms that warrant it.

At the discretion of the Investigator, other unscheduled procedures or tests may be performed if needed to ensure subject safety.

7.5.2.1. Medical and Medication History

A complete medical and medication history, as well as demographic information, will be collected at the screening visit by the Investigator or a qualified designee. The medical history will be reviewed and recorded, including:

- Date of birth
- Sex
- Race, ethnicity
- Medication history starting from 30 days prior to entering the screening period
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases
- Smoking habits

Note: Participation in previous clinical trials evaluating investigational CF therapies directed at expressing functional CFTR protein will also be recorded (eg, CFTR gene therapy studies or therapies that allow read-through of premature stop codons of CFTR gene).

7.5.2.2. Physical Examination (Including Height and Weight)

A comprehensive physical examination or limited physical examination will be performed by the Investigator or a qualified designee at the time points described in the Schedule of Procedures.

The comprehensive physical examination will include a review of the following body systems:

- General appearance

- Skin
- Head, eyes, ears, nose, and throat
- Spine/neck/thyroid
- Musculoskeletal
- Respiratory
- Cardiovascular
- Neurological
- Abdomen (including liver, spleen, and kidneys)

The limited physical examination will be driven by any new problems or issues reported by the subject since the last clinic visit or telephone contact. At minimum, the limited physical examination will include a review of the following body systems:

- Respiratory
- Cardiovascular

Abnormalities identified during the physical examination at the initial screening visit will be documented in the subject's source documents and on the medical history CRF page. Any post-baseline new or worsening abnormalities identified after the initial physical examination should be recorded on the AE CRF page, as deemed by the Investigator.

The height and weight collected at the initial screening visit will be used to calculate the subject's body mass index (BMI) using the formula below:

$$\text{BMI} = \frac{\text{Weight [kg]}}{(\text{Height [m]})^2}$$

BMI calculated at subsequent time points will continue to use the subject's height collected at the initial screening visit.

Height should be measured in centimeters (cm) and weight should be measured in kilograms (kg). Measurements should be taken in light clothing and stocking feet (without shoes) with empty pockets. The subject's height should be recorded to the nearest centimeter and weight should be recorded to the nearest 0.1 kg.

7.5.2.3. Adverse Event Collection

Refer to Section 8.1 for definitions of an AE and SAE, period of observation for the collection of AEs, and recording of AEs.

Collection of all AEs and SAEs, regardless of relationship, concomitant mediations, and concomitant surgical procedures will begin from the time the subjects signs the informed consent until study completion for each subject, which is defined as the last study assessment for that subject on Day 337 (±3 days) in Part A, Day 365 (±3 days) in Part B, or Day 341 (±3 days) in Part D of the study. As such, all AEs and SAEs will be collected throughout the study for each subject.

At each clinic visit and telephone contact during the study, subjects will be questioned in a general way to ascertain if AEs/SAEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?") or if any changes in concomitant medications had occurred. Subjects will be reminded to return to the site or call the study staff immediately if they are experiencing any symptoms of concern, either new or worsening, or were hospitalized or required a visit to the emergency department for any reason.

See Section 8.1 for more detail on follow-up of AEs to closure and reporting of AEs after the end of the study.

7.5.2.4. Vital Signs

Blood pressure, pulse rate, and body temperature will be measured at the times specified in the Schedule of Procedures. Additional blood pressure, pulse rate, and/or body temperature measurements may be performed, as determined by the Investigator, in order to ensure appropriate monitoring of subject safety and accurate recording of vital sign measurements.

Any changes from baseline that are deemed clinically significant by the Investigator are to be recorded as an AE.

Blood Pressure and Pulse Rate

The same method for obtaining blood pressure measurement (auscultatory or oscillometric) should be used throughout the study for the subject. In addition, the conditions of vital sign measurements should be controlled and as consistent as possible during the study, in order to minimize external variability of the readings. It is advised that measurements be collected at a comfortable room temperature with little to no background noise, using the same (appropriately sized) cuff placed at the same location of the same arm during the study. The cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference (a length-to-width ratio of 2:1). The bladder deflation rate should be deflated (calibrated for oscillometric method or manually by auscultatory method) at a rate of 2 to 3 mmHg/second (and the first and last audible sounds recorded as systolic and diastolic pressure) after at least 5 minutes of rest in a seated position.

The subject should be asked to remove all clothing that covers the location of cuff placement. The subject should be instructed to relax as much as possible for at least 5 minutes prior to

collection. The subject should remain quiet during this time and through the measurement. If possible, the same arm should be used for all blood pressure measurements in the study, which require only 1 reading.

The use of automated devices for measuring pulse rate is acceptable although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, blood pressure and pulse rate should be obtained prior to the nominal time of the blood collection.

During the nebulization of IP in Parts A and B only, blood pressure and pulse rate will be monitored continuously (except during rest periods) with measurements to be recorded every 5 minutes (8 mg dose level) or 10 minutes (12, 16, 20, and 24 mg dose levels), or more frequently if clinically indicated. Any changes from baseline that are deemed clinically significant by the Investigator are to be recorded as an AE.

Body Temperature

Oral temperature should be taken by placing a digital thermometer under the tongue for at least 10 seconds and the temperature reported in degrees Celsius. Other methods to measure the subject's temperature must be approved by the Sponsor.

Respiratory Rate

The respiratory rate should be taken when the subject is at rest in a comfortable position. The observer should hold the extremity of the subject as a distraction for the subject (ie, pretending he/she is taking the subject's radial pulse) and count the number of respirations for 30 seconds. The respiratory rate is reported as the number of breaths per minute.

7.5.2.5. Pulse Oximetry

Blood oxygen saturation will be measured by pulse oximetry at the times specified in the Schedule of Procedures. Additional measurements may be performed, as determined by the Investigator, in order to ensure appropriate monitoring of subject safety and accurate recording of oxygen saturation measurements. During the nebulization of IP in Parts A and B only, pulse oximetry will be monitored continuously (except during rest periods) with measurements to be recorded every 5 minutes (8 mg dose level) or 10 minutes (12, 16, 20, and 24 mg dose levels), or more frequently if clinically indicated. Any changes from baseline that are deemed clinically significant by the Investigator are to be recorded as an AE.

The index finger is the recommended site of application of the pulse oximeter sensor. Other sites include other fingers, a thumb, a toe, hand or a foot. Avoid extremities with catheters or blood pressure cuffs in place. Allow several seconds for the pulse oximeter to detect the pulse and calculate the oxygen saturation. Look for the displayed pulse indicator that shows that the machine has detected a pulse. Without a pulse signal, any readings are meaningless. Oximeters may occasionally give a false reading; if in doubt, rely on your clinical judgment, rather than the machine. Always make sure the alarms are on.

Blood oxygen saturation level measured by pulse oximetry (peripheral capillary oxygen saturation [SpO2]) will be reported as a percentage.

7.5.2.6. Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures and test-appropriate samples will be collected at the time points specified in the Schedule of Procedures. All blood samples will be collected via venipuncture. Subjects in Parts A and B will be in a fasted state (8 hours without food or drink except water) for serum chemistry study blood collections. Subjects will be at rest and in a seated or supine position during blood collection. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The Investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the Investigator or Sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

Serum Chemistry

Blood samples (approximately 8.5 mL) for serum chemistry will be collected into a serum separator tube. The following parameters will be assessed:

Albumin	Glucose
Alkaline phosphatase (ALP)	Lactate dehydrogenase
Alanine transaminase (ALT)	Magnesium
Aspartate transaminase (AST)	Phosphorus
Blood urea nitrogen	Potassium
Calcium	Sodium
Carbon dioxide (Bicarbonate)	Total and direct bilirubin
Chloride	Total protein
Creatinine	Uric acid
Creatinine kinase	C-reactive protein (CRP)
Gamma-glutamyl transferase (GGT)	

Hematology

Blood samples (approximately 4.0 mL) for hematology will be collected into an ethylenediaminetetraacetic acid (EDTA) tube. The following parameters will be assessed:

Hemoglobin (Hgb)	White blood cell (WBC) count
Hematocrit (Hct)	WBC differential (absolute and percent) • Neutrophils • Eosinophils • Monocytes • Basophils • Lymphocytes
Mean corpuscular volume (MCV)	
Mean corpuscular hemoglobin concentration (MCHC)	
Platelet count	
Red blood cell (RBC) count	

Coagulation

Blood samples (approximately 4.5 mL) for coagulation will be collected into a sodium citrate tube. The following parameters will be assessed:

Prothrombin time (PT), PT International normalized ratio (INR)
Activated partial thromboplastin time (PTT)

Urinalysis

A urine sample will be collected and analyzed for the following parameters:

pH	Bilirubin
Glucose	Nitrites
Protein	Leukocyte esterase
Blood	Specific gravity
Ketones	

Microscopic examination will be conducted if protein and/or blood is/are detected during urinalysis. At a minimum, the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

7.5.2.7. Serum Inflammatory Markers (Part B 20 mg and Part D only)

Serum samples will be analyzed for various inflammatory markers (Part B, 20 mg and Part D only), including interferon (IFN)-γ, interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and tumor necrosis factor (TNF)-α, using enzyme-linked immunosorbent assay (ELISA). The inflammatory marker testing is considered as exploratory and results will not be provided to or reviewed by the Investigator.

In addition to the time points specified in the schedule of assessments, ad hoc inflammatory marker testing may also be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events, or unexplained bronchospasm.

7.5.2.8. Pregnancy Test

A urine or serum beta-human chorionic gonadotropin (β-hCG) pregnancy test will be performed on all females, regardless of childbearing potential, at the initial screening visit, on Day -1 (Parts A and B) or Day 1 (Part D), and at discharge on Day 337 in Part A, Day 365 in Part B, or Day 341 in Part D of the study; or if pregnancy is suspected or upon withdrawal of a female subject from the study. The pregnancy test on Day -1 (Part A and Part B) or Day 1 (Part D) must be confirmed as negative before the subject can be enrolled and randomized.

7.5.2.9. Drug and Alcohol Screen

A blood or urine screen for drugs of abuse and alcohol will be performed at the initial screening visit. Additional drug and alcohol screens may be performed at the Investigator's discretion. Samples are to be tested for amphetamines, barbiturates, benzodiazepines, cocaine, methadone, opiate metabolite, and phencyclidine.

Results of drug and alcohol screens will be reviewed and verified by the study monitor, but will not be collected in the CRF. Any positive result for drugs of abuse or alcohol at the screening visit will exclude the subject from further participation in the study. Note that drug screen results that are positive for a drug of abuse may be acceptable with confirmation of valid prescription for medical use (eg, methylphenidate for the treatment of attention deficit hyperactivity disorder).

7.5.2.10. Viral Screen

At the initial screening visit, a blood sample of approximately 8.5 mL will be drawn into a serum separator tube to test for the presence of human immunodeficiency virus (HIV) type 1 or 2 antibodies, hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) antibodies.

The test results must be confirmed negative at the screening visit. If a test result is positive, the subject will be excluded from enrolling into the study. Results of the viral screen will be reviewed and verified by the study monitor but will not be collected in the CRF database.

7.5.2.11. Electrocardiogram (ECG)

ECGs will be performed at the times specified in the Schedule of Procedures. The following parameters will be recorded: heart rate, PR, QRS, QT, QTcB, and QTcF. ECG interval measurements and interpretations will be centralized and performed by a single certified cardiologist.

The ECG collected on Day -1 will serve as the subject's baseline ECG for Parts A and B. The ECG collected during Screening will serve as the subject's baseline ECG for Part D. If there is a clinically significant change from baseline, the ECG change should be reported as an AE.

7.5.2.12. Spirometry

Spirometry will be performed according to the guidelines published by the American Thoracic Society for standardization of spirometry (American Thoracic Society 1995). The following parameters will be assessed during the spirometry testing:

- Forced expiratory volume in 1 second (FEV_1): absolute volume (L) and percent predicted for age, gender, and height.
- Forced vital capacity (FVC): absolute volume (L) and percent predicted for age, gender, and height.
- FEV_1/FVC: ratio and percent predicted for age, gender, and height.
- Forced expiratory flow over the middle one-half of the FVC ($FEF_{25-75\%}$): absolute volume (L) and percent predicted for age, gender, and height.

The parameters will be normalized using the ERS Global Lung Function Initiative (GLI) prediction equations.[33] The average of the results from the testing on Day -1 and at pre-dose on Day 1 will serve as the subject's baseline for Parts A and B. The average of the results from the testing on Screening and at pre-dose on Day 1 will serve as the subject's baseline for Part D.

Instructions on Bronchodilator Use in Relation to Spirometry Testing

- If feasible for the subject, all spirometry testing should be performed "pre-bronchodilator" if the subject is receiving treatment with a short-acting beta-agonist or anticholinergic bronchodilator (eg, beta-agonist medication such as albuterol or anticholinergic agent such as ipratropium bromide). These medications should be withheld for at least 4 hours before spirometry testing.
- If the subject is receiving treatment with a long-acting bronchodilator (eg, salmeterol), these medications do not have to be withheld and spirometry testing can be performed at any time in relation to dosing with the long-acting bronchodilator.

Instructions on Subject's Routine Pulmonary Therapies in Relation to Spirometry Testing

- For testing consistency within a subject, it is suggested that all spirometry testing for a subject be consistently performed either before or after receiving their daily routine pulmonary therapies (airway clearance and pulmonary medications). It will be at the discretion of the Investigator and study staff to determine what is most feasible for each subject and to maintain this testing consistency throughout the study.

If a subject is experiencing respiratory distress or respiratory symptoms, based on the judgment of the Investigator, unscheduled spirometry testing may be performed when the subject is stable.

7.5.2.13. Chest x-ray

Chest x-rays will consist of routine posterioranterior and lateral views.

- For all subjects participating in the study, the baseline chest x-ray may be performed at any time from Day -14 to Day -2 (Parts A and B) or any time from Day -14 to Day -1 (Part D) during the screening period.

- In Part A, chest x-rays are scheduled on Day 8 and Day 29 of the study, representing intervals of 1 and 4 weeks after administration of the single dose of IP.

- In Part B, chest x-rays are scheduled on Day 36 and Day 57 of the study, representing intervals of 1 and 4 weeks after administration of the fifth dose of IP.

- In Part D, chest x-rays are scheduled on Day 11 and Day 32 of the study, representing intervals of 1 and 4 weeks after administration of the 5th dose of IP.

At the Investigator's discretion, a chest x-ray may be performed at any time during the study if the subject is experiencing respiratory symptoms that warrant it.

7.5.2.14. Measurement of [redacted] mRNA and [redacted] in Blood

See the Laboratory Manual for instructions on collection and handling of samples.

Whole blood samples will be analyzed for [redacted] mRNA and [redacted] levels. In Part A, a baseline sample will be obtained on Day -1 and post-treatment samples will be collected on Day 1 (at 8 hours), and on Days 2, 8, 15, and 29. In Part B, a baseline sample will be obtained on Day -1 and post-treatment samples will be collected on Days 2, 8 (pre-dose), 29 (pre-dose), 30, 36, 43, and 57. In Part D, a baseline sample will be obtained pre-dose on Day 1 and post-treatment samples will be collected on Day 1 (2 hours post-dose), Days 2 (pre-dose and 2 hours post-dose), 3 (pre-dose and 2 hours post-dose), 4 (pre-dose and 2 hours post-dose), 5 (pre-dose and 2 hours post-dose), 11, 18 and 32.

The quantification of [redacted] mRNA will be performed by qPCR on RNA purified from the whole blood sample. qPCR results will be reported as the number of copies of [redacted] mRNA per µg of total RNA.

The quantification of [redacted] in whole blood samples will performed by high performance liquid chromatography/mass spectrometry.

In addition to the time points specified in the schedule of assessments, ad hoc testing for measuring [redacted] mRNA and [redacted] may also be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events, or unexplained bronchospasm.

7.5.2.15. Measurement of Immune Responses to CFTR Protein

See the Laboratory Manual for instructions on collection and handling of samples.

The presence of potential antibodies to CFTR protein will be measured by an enzyme-linked immunosorbent assay in serum samples collected on Days -1 (baseline), 15, 29, 85, 169, and 337

(optional) in Part A; and on Days -1 (baseline), 36, 57, 113, 197, and 365 (optional) in Parts B; and on Days 1 (pre-dose, baseline), 11, 18, 32, 145, 229, 341 (optional) in Part D. Antibodies to PEG will also be measured.

CFTR-specific T cell responses will be assessed using peripheral blood mononuclear cells collected at the same time points. T cell responses to CFTR will be measured by a human interferon-γ enzyme-linked immunospot assay as described by Calcedo et al.[34]

As noted above, the blood collections for these assays on the final study day (Day 337 in Part A; Day 365 in Part B; Day 341 in Part D) are optional. The blood collection for any of these assays will only be taken if there has been a de novo positive result detected at one or more post-treatment time points. In the event of inconclusive, invalid, or missing assay results at the Day 169, Day 197, or Day 145 visit for Part A, Part B, or Part D, respectively, the blood collection for one or more of these assays will be taken at the final study day at the discretion of the Sponsor.

In addition to the time points specified in the schedule of assessments, ad hoc immunogenicity testing may also be performed when immunogenicity is suspected, such as febrile and/or allergy/hypersensitivity events or unexplained bronchospasm.

7.5.3. Volume of Blood to be Drawn from Each Subject

The assessments, the number of samples and sample volumes for each assessment, and total volume of blood to be drawn from each subject are presented in Appendix 4.

During Part A of the study, approximately 350.5 mL of blood will be drawn from all subjects, regardless of sex, over the duration of the study (up to 368 days or approximately 53 weeks). During Part B of the study, approximately 405.5 mL of blood will be drawn from all subjects, regardless of sex, over the duration of the study (up to 396 days or approximately 57 weeks). During Part D of the study, approximately 469.0 mL of blood will be drawn from all subjects, regardless of sex, over the duration of the study (up to 372 days or approximately 54 weeks). These volumes include the optional blood samples to be collected on the final study day (Day 337 in Part A; Day 365 in Part B; Day 341 in Part D), if needed for assessment of immune responses to CFTR protein (Section 7.5.2.15).

When more than one blood assessment is to be done at the time point, the assessments may be combined if they require the same type of tube.

The total amount of blood to be drawn is an estimate, as it may vary depending on the study center's sample volume requirements for the safety tests (serum chemistry, hematology, coagulation, CRP), pregnancy test (β-hCG), and viral screen (HIV, HBsAg, and HCV tests).

7.5.4. Cystic Fibrosis Questionnaire-Revised (CFQ-R)

The Cystic Fibrosis Questionnaire-Revised (CFQ-R; version for adolescents and adults [patients 14 years old and older]) will be completed by Part B subjects at baseline on Day -1, and on Days 36, 43, 57, 85, 113, 197, 281, and 365.[35] The results of the respiratory domain of the CFQ-R will

be of primary interest; the minimal change from baseline representing a clinically important improvement in the respiratory domain was determined to be ≥4.[36]

7.6. Coronavirus Disease Contingency Measures

Consistent with FDA Guidance on the conduct of clinical trials during the coronavirus disease (COVID-19) public health emergency (March 2020), ensuring the safety of trial participants is paramount. Public health measures implemented by Federal and State authorities to control the COVID-19 pandemic have made compliance with protocol-mandated in-person study visits unfeasible. As such, protocol-mandated in-person study visits may be conducted as telephone visits to query the subject about the occurrence of any AEs/SAEs and any changes in concomitant medications or surgical procedures. Such changes from the protocol will be captured as protocol deviations due to COVID-19.

For subjects participating in Part A, the clinic visits at Day 29 and Day 337 are the highest priority and should be conducted in-person within 4 weeks of the target visit date, if possible.

For subjects participating in Part B, other than the clinic visits on dosing days (which are mandatory), clinic visits during the treatment period (through Day 30), as well as at Days 36, 57, and 365 are the highest priority and should be conducted in-person within 4 weeks of the target visit date, if possible.

For subjects participating in Part D, other than the clinic visits on dosing days (which are mandatory), the clinic visits at Day 11, Day 32, and Day 341 are the highest priority and should be conducted in-person within 4 weeks of the target visit date, if possible.

At the discretion of the Sponsor and with subject consent, planned onsite visits (excluding dosing visits) may be conducted at the subject's home (or designated space) by a study coordinator or qualified home health professional, as available. Assessments conducted at these visits will be focused on patient safety and may include collection of safety labs, vital signs, ECG, adverse events, concomitant medications/surgical procedures.

As the epidemiological conditions and risks may differ across different geographies in the United States, the threat of COVID-19 may differ at each clinical site. Once the risk has diminished in a particular region as determined by Federal and State public health officials and subjects and site staff are comfortable returning to in-person visits, all protocol-mandated in-person study visits should resume as planned.

8. ADVERSE AND SERIOUS ADVERSE EVENT ASSESSMENT

8.1. Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. If a pulmonary exacerbation is suspected, sufficient information should be recorded to determine if the event can be classified as a pulmonary exacerbation based on the criteria defined in Section 8.1.7. All AEs should be captured on the appropriate AE pages in the CRF and in source documents. In addition to untoward AEs, unexpected benefits outside the IP indication should also be captured on the AE CRF.

All AEs and SAEs, regardless of relationship, will be collected for each subject from the time the subject signs the informed consent until study completion, which is defined as the last study assessment for that subject on Day 337 (±3 days) in Part A, Day 365 (±3 days) in Part B, or Day 341 (±3 days) in Part D of the study. As such, all AEs and SAEs will be collected throughout the study for each subject.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

If the Investigator considers it necessary to report an AE in a study subject after the end of the study, he or she should contact the Medical Monitor to determine how the AE should be documented and reported.

8.1.1. Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of IP, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of IP, but the dyspepsia becomes severe and more frequent after first dose of IP has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate CRF).

The Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (Published: May 28, 2009 [v4.03: June 14, 2010]), should be referenced when assessing the severity of an AE. If an AE is not described in the CTCAE, the severity should be recorded based on the scale below:

Severity (Grade)	Definition
Mild (Grade 1)	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate (Grade 2)	A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.
Severe (Grade 3)	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.
Life-Threatening (Grade 4)	Life-threatening consequences; urgent intervention indicated.
Death (Grade 5)	Death related to AE

A life-threatening event (Grade 4 severity) is defined as an AE in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe (Section 8.2.3).

8.1.2. Relationship Categorization

Relationship of an AE or SAE to IP is to be determined by the Investigator based on the following definitions:

Relationship to IP	Definition
Not Related	Unrelated to IP.
Possibly Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of IP, but which could also be explained by concurrent disease or other drugs or chemicals.
Probably Related	A clinical event or laboratory abnormality with a reasonable time sequence to administration of IP, unlikely to be attributable to concurrent disease or other drugs and chemicals and which follows a clinically reasonable response on de-challenge. The association of the clinical event or laboratory abnormality must also have some biological plausibility, at least on theoretical grounds.
Definitely Related	The event follows a reasonable temporal sequence from administration of the IP, follows a known or suspected response pattern to the IP, is confirmed by improvement upon stopping the IP (de-challenge), and reappears upon repeated exposure (re-challenge). Note that this is not to be construed as requiring re-exposure of the subject to IP; however, the determination of definitely related can only be used when recurrence of the event is observed.

8.1.3. Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4. Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory test, vital sign, ECG parameter, or other safety assessment (eg, oxygen saturation by pulse oximetry, spirometry testing, chest x-ray) can represent an AE if the change is clinically relevant or if, during treatment with the IP, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the IP, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory, vital sign, or ECG values, or abnormal values in any other safety assessments which were not present at the pretreatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory, vital sign or ECG parameter, or a change in any other safety assessment performed in the study is clinically significant and therefore represents an AE.

8.1.4.1. Evaluation of Elevations in Liver Function Tests

Subjects meeting any of the 3 criteria listed below must be followed closely with repeat confirmatory testing within 48 to 72 hours of the initial finding (should include ALT, AST, ALP, GGT, INR, and total bilirubin testing) to determine if these parameters are increasing or decreasing. Subjects should be followed closely for clinical progression and there should be monitoring of ALT, AST, ALP, GGT, INR, and total bilirubin levels, as clinically indicated. Subjects should be followed until their transaminases and other laboratory parameters normalize or return to baseline.

- Elevation of ALT or AST to >5x ULN in a subject regardless of baseline value
- Elevation of ALT or AST to >3x ULN in a subject with a normal baseline or elevation of >3x ULN from the subject's actual baseline if not normal, with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- Elevation of ALT or AST to >3x ULN in a subject with a normal baseline or elevation of >3x ULN from the subject's actual baseline if not normal, and total bilirubin >2x ULN or INR >1.5.

If any of the above criteria is met by a Part B or Part D subject who has not completed dosing with IP, treatment must be interrupted immediately and the Medical Monitor notified of this action.

A thorough investigation of other potential causes should be conducted in all cases. If no convincing alternative etiology (eg, pre-existing CF-related liver disease, viral hepatitis, alcohol ingestion, concomitant medication [such as antibiotic treatment]) for the elevated transaminases and symptoms is identified, regardless of whether ALT or AST levels have improved, treatment of the subject must be discontinued, in consultation with the Medical Monitor. If a convincing alternative etiology for the elevated transaminases is identified and the subject's symptoms and laboratory findings have improved, the Investigator may consider resuming IP treatment with close monitoring, in consultation with the Medical Monitor.

8.1.4.2. Development of Immune Responses to CFTR Protein or PEG

In addition to the time points specified in the schedule of assessments, immunogenicity testing will also be performed when immunogenicity is suspected, such as allergy/hypersensitivity events or unexplained bronchospasm.

8.1.5. Pregnancy

All pregnancies are to be reported from the time the subject signs the informed consent until the final study visit on Day 337 (±3 days) in Part A, Day 365 (±3 days) in Part B, or Day 341 (±3 days) in Part D of the study.

Any report of pregnancy for any female study participant or the partner of a male study participant must be reported within 24 hours to Rho Product Safety. The pregnancy report and any applicable follow-up information will also be sent to the Medical Monitor by Rho Product Safety. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported to Rho Product Safety (Section 8.2.2). Note: An elective abortion for non-medical reasons is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy complication meets serious criteria, it must be reported as an SAE to Rho Product Safety (Section 8.2.2). The test date of the first positive serum β-hCG test or ultrasound result will determine the pregnancy onset date.

8.1.6. Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the Sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of IP when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- **Misuse** – Intentional use of IP other than as directed or indicated at any dose (Note: this includes a situation where the IP is not used as directed at the dose prescribed by the protocol)
- **Overdose** – Intentional or unintentional intake of a dose of IP higher than the protocol-prescribed dose
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an IP. For studies, medication errors are reportable to the Sponsor only as defined below.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of the unassigned treatment is/are always reportable as a medication error.

The administration and/or use of an expired IP should be considered as a reportable medication error.

8.1.7. Classification of Events as Pulmonary Exacerbations

The number of pulmonary exacerbations experienced by subjects will be assessed in this study. A pulmonary exacerbation will be defined as a new or change in antibiotic therapy (intravenous, inhaled, or oral) for a subject experiencing any 4 or more of the following signs or symptoms according to the modified Fuchs criteria presented by Ramsey et al.[37]

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of pulmonary infection

In addition to pulmonary exacerbations defined by the above criteria, physician-reported pulmonary exacerbations will also be recorded. Severity of pulmonary exacerbations will be scored according to the general principles described in Section 8.1.1.

8.1.8. Adverse Events of Special Interest

An AESI can be serious or nonserious. Ongoing monitoring and rapid communication (within 24 hours) by the Investigator to the Sponsor is required to allow for further characterization and reporting to the PSRC and regulatory authorities (as required). The Investigator should report all AESIs within 24 hours on the AE CRF in the EDC system.

8.1.8.1. Allergic/Hypersensitivity Reactions

A suspected moderate to severe allergic/hypersensitivity reaction, including but not limited to anaphylaxis, generalized rash, edema or bronchospasm deemed possibly related to study drug is an AESI for MRT5005. The study site should report the occurrence of such a reaction to the

Sponsor within 24 hours of their first knowledge of the event and record the details of the event on the AE CRF in the EDC system.

8.2. Serious Adverse Event Procedures

8.2.1. Reference Safety Information

The reference for safety information for this study is the current MRT5005 Investigator's Brochure, which Translate Bio has provided under separate cover to all Investigators.

8.2.2. Reporting Procedures

All SAEs must be reported by the Investigator to Rho Product Safety, through the EDC system, within 24 hours of the first awareness of the event. The Medical Monitor will be notified of the SAE by Rho Product Safety. In the event of a fatal or life-threatening SAE, the Investigator must contact the Medical Monitor immediately by phone. The SAE must also be entered into the EDC system as soon as possible to notify Rho Product Safety.

Medical Monitor:

[redacted]

Responsible Physician:

[redacted]

Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (Section 8.1.6) unless they result in an SAE.

If there are any questions regarding the reporting of SAEs, the Investigator should contact Rho Product Safety. For protocol- or safety-related issues, the Investigator should contact the Medical Monitor.

Rho Product Safety:

SAE Help Line: 888-746-7231 or 919-595-6486

Safety E-mail: rho_productsafety@rhoworld.com

8.2.3. Serious Adverse Event Definition

A **Serious Adverse Event (SAE)** is any untoward medical occurrence (whether considered to be related to IP or not) that at any dose:

- Results in death

- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously planned or scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. Hospitalizations for prophylactic antibiotic therapy and respiratory treatment (eg, CF cleanouts) should also not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).

- Results in persistent or significant disability/incapacity

- Is a congenital abnormality/birth defect

- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4. Suspected Unexpected Serious Adverse Reaction

A SUSAR is a Serious Adverse Reaction that is not listed in the Investigator's brochure or is not listed at the specificity or severity that has been observed; or, if an Investigator's brochure is not required or available, is not consistent with the risk information described in the General Investigational Plan or Investigator's Brochure. Adverse Drug Reaction is defined as an Adverse Event with a reasonable plausibility of drug related causality.

8.2.5. Serious Adverse Event Collection Time Frame

All SAEs, regardless of relationship, will be collected for each subject from the time the subject signs the informed consent until study completion, which is defined as the last study assessment for that subject on Day 337 (±3 days) in Part A, Day 365 (±3 days) in Part B, or Day 341 (±3 days) in Part D of the study. As such, all SAEs will be collected throughout the study for each subject.

As described in Section 8.2.2, all SAEs must be reported by the Investigator to Rho Product Safety, through the electronic data capture (EDC) system, within 24 hours of the first awareness of the event. The Medical Monitor will be notified of the SAE by Rho Product Safety. In the

event of a fatal or life-threatening SAE, the Investigator must contact the Medical Monitor immediately by phone.

In addition, any SAE(s) considered "related" to the IP and discovered by the Investigator at any interval after the study has been completed must be reported to the Rho Product Safety and the Medical Monitor within 24 hours of the first awareness of the event.

If the Investigator considers it necessary to report an SAE in a study subject after the end of the study, he or she should contact the Medical Monitor to determine how the SAE should be documented and reported.

8.2.6. Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.7. Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another IP action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the IP should be recorded as "dose not changed" or "not applicable" (if the subject never received IP). The IP action of withdrawn should not be selected solely as a result of the subject's death.

8.2.8. Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor is responsible for notifying the relevant regulatory authorities and the site is responsible for promptly notifying the relevant IRB of related, unexpected SAEs.

In addition, the Sponsor is responsible for notifying active sites of all unexpected SAEs related to MRT5005 occurring during all interventional studies across the MRT5005 program.

The Investigator is responsible for notifying the local IRB, local ethics committee, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1. Data Collection

The Investigators' authorized site personnel must enter the information required by the protocol on the CRF. A study monitor will visit each site in accordance with the monitoring plan and review the CRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the CRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the Investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the CRF entry within approximately 2 to 3 business days of the subject's visit.

9.2. Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3. Data Handling Considerations

Data that may potentially unblind the treatment assignment (ie, IP blood concentrations, antibodies to IP, treatment allocation, IP preparation/accountability data) will be handled with special care during the data cleaning and review process. These data will be handled in such a way that, prior to unblinding, any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

9.4. Statistical Analysis Process

The study will be analyzed by the Sponsor or its agent.

The statistical analysis plan will provide the statistical methods for the analysis of the safety data as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, IP exposure, and prior and concomitant medications. Subjects randomized to placebo in each dose level group (single or multiple-dose) will be combined and presented as placebo, and subjects randomized to the active product will be combined and presented for each MRT5005 dose level (single or multiple-dose).

To preserve the integrity of the statistical analysis and study conclusions, the statistical analysis plan will be finalized prior to database lock.

All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC 27513).

9.5. Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There are no planned data monitoring committee meetings for this study, but a PSRC will review safety data, as explained in Section 3.4.1. In addition, there is a Sponsor-independent data monitoring committee (DMC) affiliated with the Cystic Fibrosis Foundation to safeguard the interests of study participants in conjunction with PSRC. The DMC has a representative member on the PSRC who reports back to the DMC potential safety signals that require a wider discussion with CF experts.

An adaptive design is incorporated as described below and in Sections 3.1 and 3.2.

- Part A: Based on the judgment of the PSRC, a single-dose group in Part A may be repeated to further assess the safety of the dose level prior to dose escalation and/or before multiple dosing is allowed to proceed in Part B.

The blind will be maintained in the 8, 16, and 24 mg single dose groups in Part A until the 1-month timepoint after the last dose (Day 29) of the last subject in the 24 mg dose group. The blind will be maintained in the 20 mg single dose group, as well as the 8, 16, and 12 mg multiple dose groups in Part B until the 1-month timepoint after the last dose (Day 57) of the last subject dosed in the 12 mg multiple dose group. For the 20 mg multiple dose group in Part B (if applicable), the blind will be maintained until the last subject in this group has reached the 1-month timepoint after the last dose day (Day 57). For Part D, the blind will be maintained until the 1-month timepoint after the last dose (Day 32) of the last subject in Part D. After that point, the data will be gathered in an unblinded fashion for the remainder of the study duration, to enable a better evaluation of the relatedness of observed AEs to the drug treatment. Details will be provided in the SAP.

Four interim analyses are planned and will include data as follows:

- All available data for the 8, 16, and 24 mg single dose groups in Part A, including at least four weeks of data (Day 29) following the 4th subject dosed in the 24 mg single dose group.
- All available data for the 8, 16, and 12 mg multiple dose groups in Part B, including at least four weeks of data following the last dose (Day 57) of the last subject dosed in these dose groups. All available data for the 8, 16, 20, and 24 mg single dose groups in Part A through four weeks of data (Day 29) for all subjects.
- All available data for Part D, including at least four weeks of data following the last dose (Day 32) of the last subject in Part D.
- All available data for all groups in Part B, including at least 6 months of data following the last dose (Day 197) of the last subject in Part B.

These interim data will be used to inform decisions related to the dose and design of Phase 2 studies. Details of the interim analyses will be provided in the interim analysis plan.

9.6. Sample Size Calculation and Power Considerations

The sample size is not based on any statistical considerations. The sample size is based on traditional Phase 1 first-in-human study designs for this disease population. In Parts A and B of the study, the inclusion of 4 subjects per dose group (3 subjects randomized to MRT5005 and 1 subject randomized to placebo) will provide basic information on safety and tolerability during dose escalation of MRT5005. In Part D, subjects treated 4 mg MRT5005 or placebo will provide further safety and tolerability data on MRT5005.

As described in Section 9.5, this study is also designed with the flexibility to enroll additional groups of subjects to support meeting its objectives.

9.7. Analysis Populations

The primary analysis population for safety will be the safety analysis set, which will include all randomized subjects who received IP. For all safety analyses, subjects will be analyzed according to the treatment they actually received.

9.8. Analyses

All analyses will use descriptive rather than inferential approaches given the objectives of the study. All summaries will be displayed by treatment group. Summary statistics for continuous variables will include the sample size (N), mean, standard deviation, minimum, median, and maximum. For categorical data, summaries will include the frequency and percentage.

9.8.1. Safety Analyses

Full details of the safety analyses will be provided in the statistical analysis plan.

Subject disposition, demographics and baseline characteristics, IP exposure, and prior and concomitant medications will be summarized. Adverse events will be coded using the MedDRA. The number and percentage of subjects with treatment-emergent AEs will be calculated overall, by system organ class, by preferred term, and by treatment group. Treatment-emergent AEs will be further summarized by severity and relationship to IP. Adverse events related to IP, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized or listed. The number and incidence of pulmonary exacerbations will be analyzed by treatment group. Results from vital sign measurements, clinical laboratory tests, ECGs, spirometry testing, pulse oximetry, and chest x-rays will be summarized by treatment, dose group, and visit. Clinically important findings will also be summarized or listed.

9.8.2. Other Analyses

Details of other analyses (eg, analysis of the CFQ-R) will be provided in the statistical analysis plan.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third party vendor (eg, contract research organization) used in this study will be maintained in the Investigator's and Sponsor's files, as appropriate.

10.1. Sponsor's Responsibilities

10.1.1. Good Clinical Practice Compliance

The study Sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study Sponsor and/or the company organizing/managing the research on behalf of the Sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and inter/national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Sponsor ensures that local regulatory authority requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of IP for shipment to the site.

10.1.2. Indemnity/Liability and Insurance

The Sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied to the Investigator as necessary.

10.1.3. Public Posting of Study Information

The Sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating Investigators' names and contact information.

10.1.4. Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The Sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.5. Study Suspension, Termination, and Completion

The Sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2. Investigator's Responsibilities

10.2.1. Good Clinical Practice Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the Investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks, and shall, upon request of the Sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for Investigators and sub-Investigators are provided to the study Sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the Investigator should, with the subject's consent, inform them of the subject's participation in the study.

The coordinating principal Investigators will review the final clinical study report. Agreement with the final clinical study report is documented by the signed and dated signature of the coordinating principal Investigators, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2. Protocol Adherence and Investigator Agreement

The Investigator and any co-Investigators must adhere to the protocol as detailed in this document. The Investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an Investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the Investigator suspends or terminates the study at their site, the Investigator will promptly inform the Sponsor and the IRB/EC and provide them with a detailed written explanation. The Investigator will also return all IP, containers, and other study materials to the Sponsor. Upon study completion, the Investigator will provide the Sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the Sponsor, applicable contract research organization, Investigator, or for multicenter studies, the coordinating principal Investigator according to national provisions and will be documented in the Investigator agreement.

10.2.3. Documentation and Retention of Records

10.2.3.1. Case Report Forms

Case report forms (CRFs) are supplied by the Sponsor or Sponsor designee and should be handled in accordance with instructions from the Sponsor.

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded to CRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Case report forms must be completed by the Investigator or designee as stated in the site delegation log.

All data will have separate source documentation; no data will be recorded directly onto the CRF.

All data sent to the Sponsor must be endorsed by the Investigator.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2. Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to subject's medical file, study-related print-outs (eg, ECGs), and original clinical laboratory and test reports.

All key data must be recorded in the subject's medical records.

The Investigator must permit authorized representatives of the Sponsor, the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the CRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, chest x-rays).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, the Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the Sponsor.

10.2.3.3. Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the Sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4. Financial Disclosure

The Investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the Investigator received from the Sponsor. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in IP; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54.2(b) (1998).

10.3. Ethical Considerations

10.3.1. Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal Investigator provides the Sponsor with a copy of the consent form which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the Sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, Sponsor or coordinating principal Investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

10.3.2. Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

For sites within the EU, the applicant for an EC opinion can be the Sponsor, the Investigator, or for multicenter studies the coordinating principal Investigator or Sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the clinical trial agreement.

Prior to implementing changes in the study, the Sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

IP supplies will not be released until the Sponsor has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the Investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the Sponsor, the Investigator or for multicenter studies the coordinating principal Investigator, according to national provisions. The Investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4. Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with HIPAA of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the Sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the Sponsor and/or its representatives' reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market MRT5005; national or local regulatory authorities; and the IRB/EC which gave approval for the study to proceed. The Sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the Sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies - containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth - will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5. Study Results / Publication Policy

Translate Bio will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Translate Bio adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Translate Bio products or projects must undergo appropriate technical and intellectual property review, with Translate Bio agreement to publish prior to release of information. The review is aimed at protecting the Sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal Investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal Investigator has such sole, joint or shared rights, the principal Investigator grants the Sponsor a perpetual, irrevocable, royalty-free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the Investigator shall have the right to publish the study results, and any background information provided by the Sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the Sponsor's confidential information shall be submitted for publication without the Sponsor's prior written agreement to publish, and shall be given to the Sponsor for review at least 60 days prior to submission for publication. If requested in writing by Translate Bio, the institution and principal Investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the Sponsor in conjunction with the Sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the Sponsor within an 18-month period after conclusion, abandonment,

or termination of the study at all sites, or after the Sponsor confirms there shall be no multicenter study publication of the study results, an Investigator may individually publish the study results from the specific site in accordance with this section. The Investigator must, however, acknowledge in the publication the limitations of the single-site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors current standards. Participation as an Investigator does not confer any rights to authorship of publications.

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12. PROTOCOL AMENDMENTS

The below table describes any substantial changes applied to the protocol since the previous version (Version 4.0, dated 29 July 2019). In addition to these changes, various non-substantial changes have been made (including but not limited to correction of typographical errors, formatting, and edits which do not affect the safety of subjects, or the scientific value or conduct of the study).

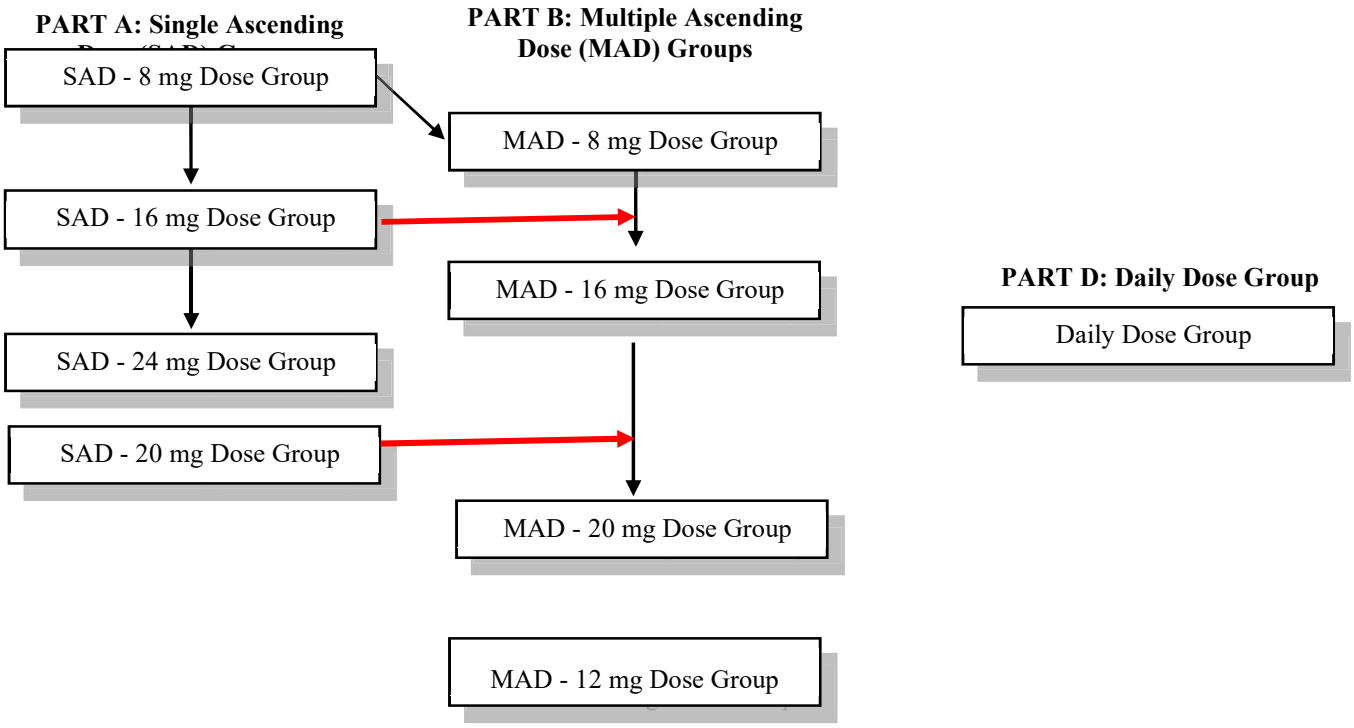
Protocol Amendment 4 (Version 5.0), dated 30 July 2020

Description of Substantial Change	Section(s) Affected
Replaced Part B Expansion with new Part D to evaluate the safety of 5 consecutive daily doses of 4 mg MRT5005/placebo in 8 subjects.	Synopsis Tables 8 and 9 Section 2.2 Section 2.2.3 Section 3.2.3 Section 7.3 Appendix 1 Appendix 4
A digital thermometer will be provided to remaining subjects enrolled in the study (Part B 12 mg, Part B 20 mg, Part D). Subjects will be instructed to self-record body temperature in a paper diary at regular intervals on each dosing day in order to document the occurrence of fevers on each dosing day.	Synopsis Tables 4 and 8 Section 7.2.2 Section 7.3.2
Split Exclusion Criterion #4 into 2 separate criteria to clarify that concomitant KALYDECO is exclusionary for all study parts, whereas concomitant TRIKAFTA is exclusionary for Parts A and B only.	Synopsis Section 4.2
Based on the observation of a potential hypersensitivity reaction in the Part A, 20 mg dose group, broadened the individual stopping rule for hypersensitivity reactions per PSRC and DMC recommendation.	Section 4.5.1
Added new dose group stopping criterion for potential hypersensitivity reaction per PSRC and DMC recommendation.	Section 4.5.4
Per PSRC and DMC recommendation, designated potential hypersensitivity reactions as adverse events of special interest requiring rapid communication to Sponsor and notification of PSRC in real-time.	Section 8.1.8
Added a new inflammatory marker panel to measure IFN-γ, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and TNF-α in Part B 20 mg and Part D.	Tables 1-9 Section 7.5.2.7
Removed requirement from Inclusion Criterion #10 for withholding rhDNase (PULMOZYME) for 24 hours before and after administration of IP based on the results of an in vitro study concluding that there is no effect of Pulmozyme on MRT5005 stability.	Synopsis Section 4.1

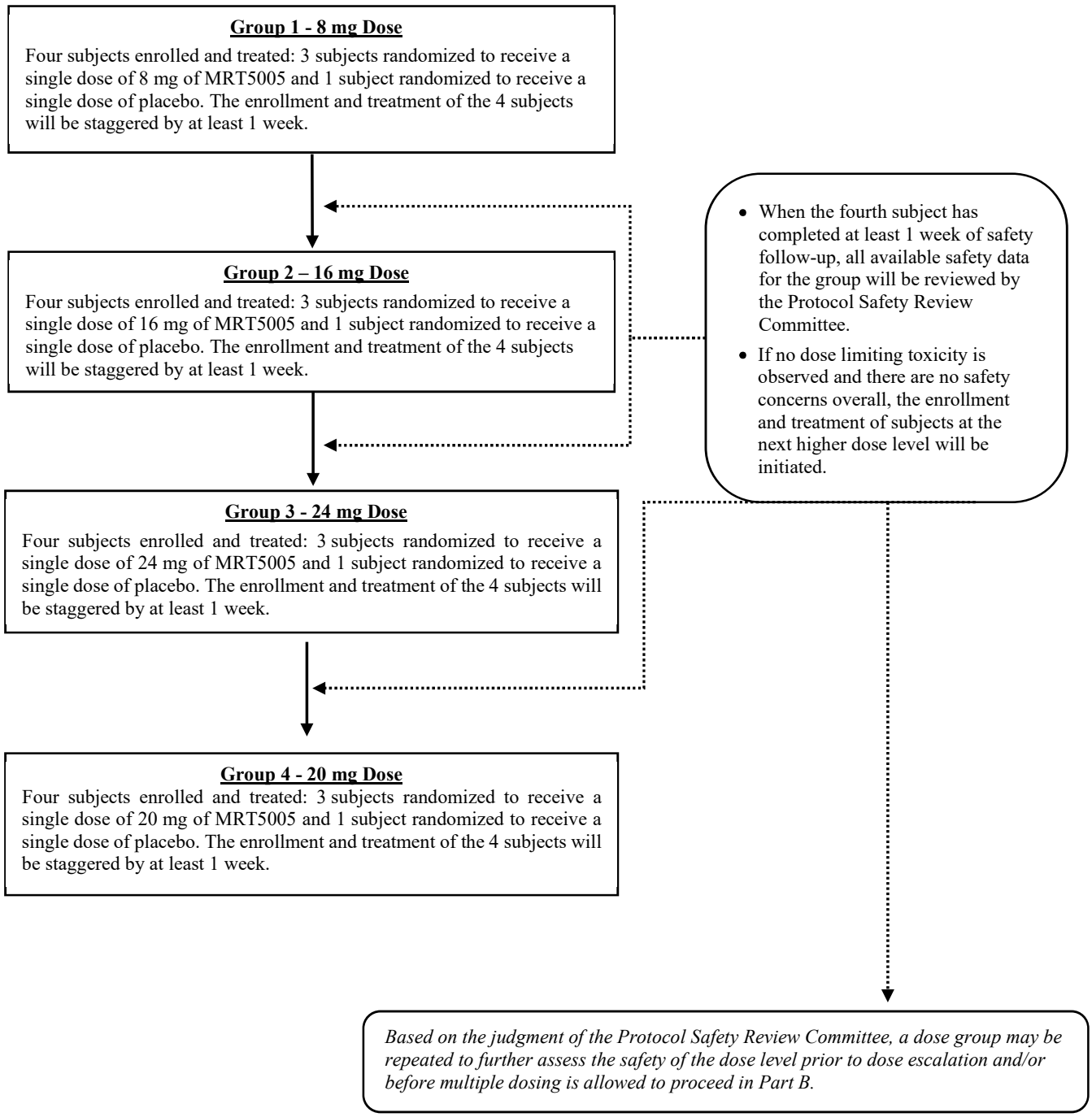
13. APPENDICES

APPENDIX 1. ENROLLMENT AND TREATMENT ALLOCATION

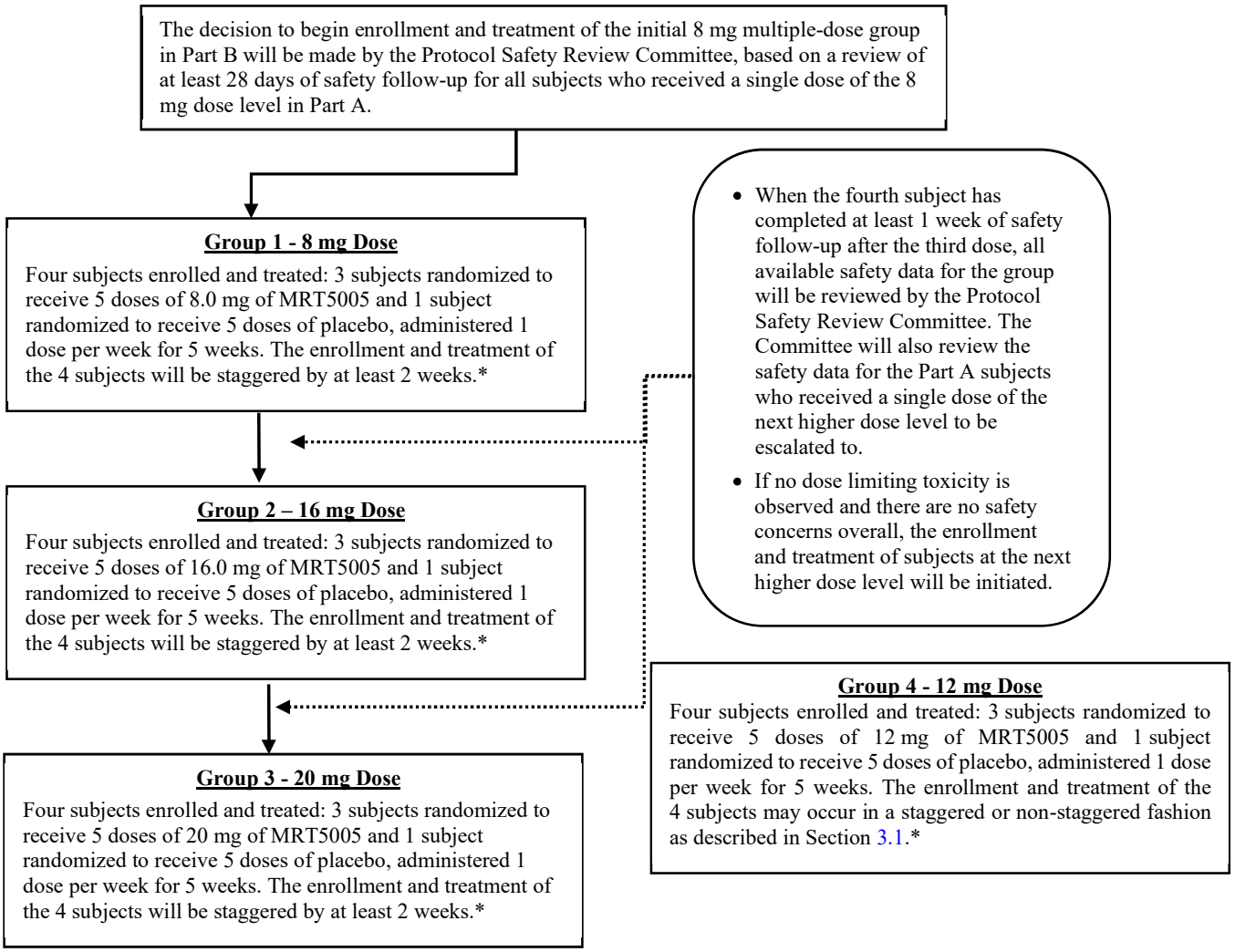
Overview of Subject Enrollment and Treatment Allocation



Part A: Safety Assessment of Single Ascending Doses (SAD)



Part B: Safety Assessment of Multiple Ascending Doses (MAD) of MRT5005



*The next subject in the dose group will only be enrolled and treated when the previous subject has received their second dose and there is at approximately 1 week of safety follow-up.

APPENDIX 2. CLASSIFICATION OF CFTR GENE MUTATIONS

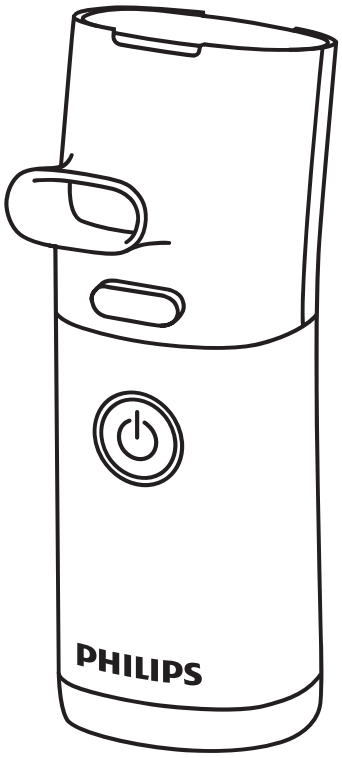
Category	Mutation	Specific mutations
Class I	Defective Protein Synthesis (nonsense, frameshift, aberrant splicing)	1078delT, 1154 insTC, 1525-2A > G, 1717-1G > A, 1898+1G > A, 2184delA, 2184 insA, 3007delG, 3120+1G > A, 3659delC, 3876delA, 3905insT, 394delTT, 4010del4, 4016insT, 4326delTC, 4374+1G > T, 441delA, 556delA, 621+1G > T, 621-1G > T, 711+1G > T, 875+1G > C, E1104X, E585X, E60X, E822X, G542X, G551D/R553X, Q493X, Q552X, Q814X, R1066C, R1162X, R553X, V520F, W1282X, Y1092X
Class II	Abnormal Processing and Trafficking	A559T, D979A, ΔF508, ΔI507, G480C, G85E, N1303K, S549I, S549N, S549R
Class III	Defective Channel Regulation/Gating	G1244E, G1349D, G551D, G551S, G85E, H199R, I1072T, I48T, L1077P, R560T, S1255P, S549 (R75Q)
Class IV	Decreased Channel Conductance	A800G, D1152H, D1154G, D614G, delM1140, E822K, G314E, G576A, G622D, G85E, H620Q, I1139V, I1234V, L1335P, M1137V, P67L, R117C, R117P, R117H, R334W, R347H, R347P, R347P/R347H, R792G, S1251N, V232D
Class V	Reduced Synthesis and/or Trafficking	2789+5G > A, 3120G > A, 3272-26A > G, 3849+10kbC > T, 5T variant, 621+3A > G, 711+3A > G, A445E, A455E, IVS8 poly T, P574H

Note: For the purposes of this protocol, 875+1G >C will be considered a Class V mutation.
Source: Publication by Green et al.[38]

APPENDIX 3. INSTRUCTION MANUAL: INNOSPIRE GO NEBULIZER

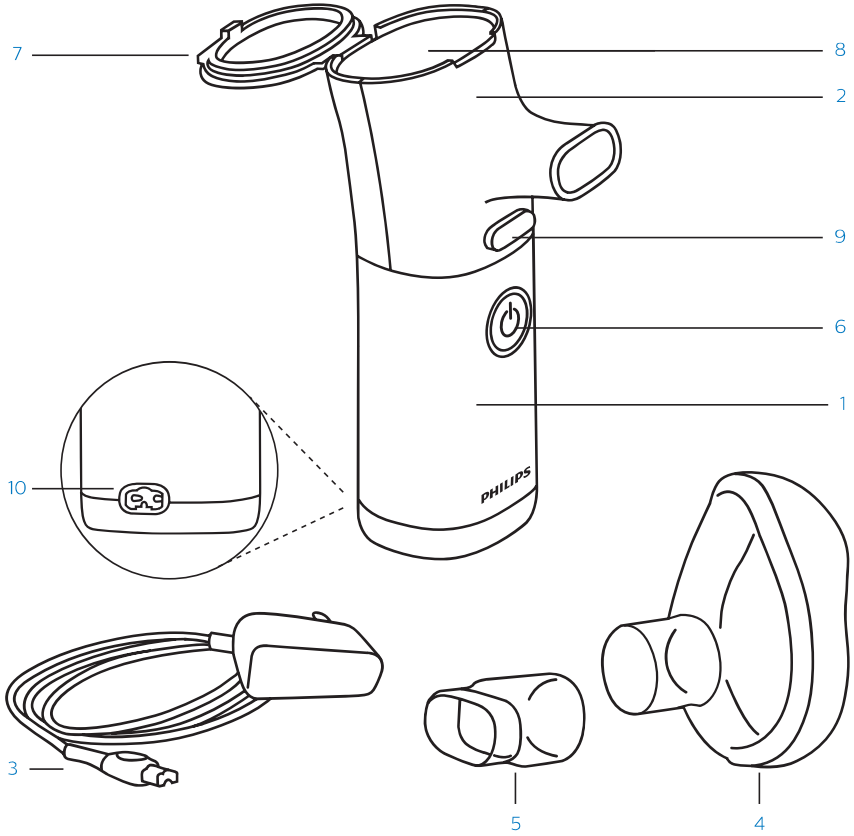
PHILIPS

InnoSpire Go
イノスパイア ゴー



InnoSpire Go

Mesh nebulizer system



Index

1. Handset
2. Mouthpiece assembly
3. AC power adapter
4. LiteTouch medium mask (age 2 - 5 years)
5. Mask adapter
6. On/Off button and LED indicator
7. Medication chamber lid
8. Medication chamber
9. Mouthpiece assembly release button
10. Power socket (back view)
11. Carry case (not shown)

Instructions for use

Please read these instructions carefully before first use. If you do not understand any portion of these instructions, contact your healthcare provider or call Philips Customer Service at 1-724-387-4000.

General information

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician or licensed healthcare professional.

Intended use: The InnoSpire Go is a vibrating mesh nebulizer system designed to aerosolize liquid medications for inhalation by the patient. The device may be used with pediatric (2 years and older), defined by the prescribed medication, and adult patients in the home environment or in a hospital/clinic setting.

⚠ Keep these Instructions for future reference

Retain carton and packing materials for storing the unit or for product returns.

⚠ Cautions

It is recommended to have a backup device (e.g. MDI) for respiratory delivery in case a situation arises when your nebulizer cannot be used.

- InnoSpire Go is intended for SINGLE PATIENT USE, to deliver multiple doses.
- It is not to be used by patients that are unconscious or not breathing spontaneously.
- The patient or the patient's care giver is the intended operator of the device.
- Only use this nebulizer with medications prescribed by your physician.
- Do not place or store the product where it can fall into water.
- Do not submerge the handset in water or other liquid cleaning agents.
- If the handset is accidentally dropped into a liquid, immediately disconnect the AC adapter from the wall outlet, prior to removing the handset from the liquid.
- Any liquid spilled on the handset should be allowed to dry before operating.
- Do not position the product where it is difficult to disconnect the plug.
- Adult supervision is necessary when this product is used by, on, or near children or physically challenged individuals or individuals with learning difficulties.

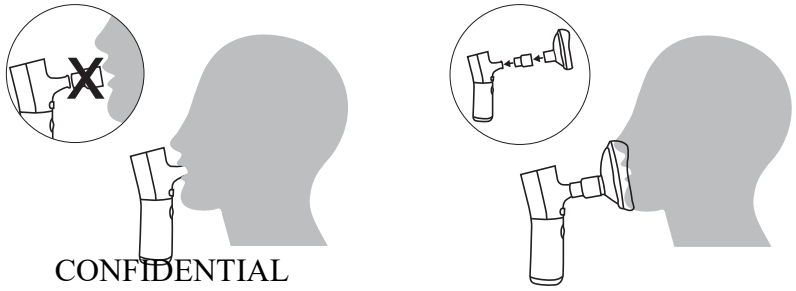
- Use this product only for its intended use as described in this manual. Failure to do so may compromise performance. Only use accessories provided with the nebulizer and recommended by the manufacturer. Store in a clean place out of the reach of children.
- Do not disassemble or modify the nebulizer in anyway. There are no serviceable parts. The battery is non-replaceable.
- The battery has been fitted at the date indicated on the unit carton and has a shelf life of 18 months past this date.
- Never charge or operate this product if it has a damaged cord or plug, if it is not working properly, if it has been dropped or damaged, or dropped into water.
- Do not connect to other equipment not described in these instructions.
- Do not charge your device on an aircraft.
- Keep the power cord away from heated surfaces.
- The nebulizer must be operated using the specified power sources.
- Always check the inside of the mouthpiece assembly or mask for any debris before use.
- Do not use while operating a vehicle.
- Never use when lying down.
- When operated at an ambient temperature 40°C/104°F the handset can reach temperatures of up to 43°C/109°F. The device should not be used for more than 10 minutes during this scenario.
- Do not use in an anesthetic or ventilator breathing system.
- InnoSpire Go and all its parts (including battery) must be disposed of properly and according to the local regulations in force (for example the WEEE directive).
- Small parts can be inhaled or swallowed. In addition, the cable, due to its length, may result in provoking strangulation or asphyxiation. Do not leave the device alone with a small child or physically challenged individual or individual with learning difficulties.
- The nebulizer should not be used around flammable substances e.g. oxygen, nitrous oxide, or in the presence of a flammable anesthetic mixture.
- Never poke the mesh, or clean it with any sharp objects. This could damage the mesh and prevent your device from operating properly.
- Do not autoclave the device.
- Report unexpected operation or events to Philips.
- Precautions are to be taken in the event of changes in the performance of the device, please refer to the troubleshooting section.

How to use your InnoSpire Go

1. After unpacking the nebulizer check you have all the items listed and that there is no visible damage or defects. Contact your product distributor or Philips customer service if anything is missing or damaged. Prior to first use clean the mouthpiece assembly as per the cleaning instructions and fully charge the battery. Ensure the device is disconnected from the power during assembly and disassembly.

2. Check the nebulizer and accessories are clean (free of debris), dry and not damaged prior to use.
3. Attach the mouthpiece assembly to the handset. Do not use separate mask adapter as a mouthpiece.
4. Lift the green medication chamber lid.
5. Empty the contents of the medication vial into the medication chamber.
   - The maximum fill volume is 8ml and this is shown by the word MAX on the protrusion below the hinge. **Do not fill medication above this level.**
6. Close the lid to the medication chamber.
7. If using a mask, attach the mask adapter to the mouthpiece assembly and attach the mask to mask adapter.
8. If you are using the power adapter to power the nebulizer, plug the cable into the socket on the handset and plug the adapter into the wall outlet.
9. Press the on/off button on the handset to switch the nebulizer on and begin nebulization.
10. Check the battery level.
    - If the LED is **SOLID GREEN** the battery is charged.
    - If the LED is **SOLID AMBER**, there is enough charge for at least one more treatment. Please charge your nebulizer after your treatment.
    - If the LED **FLASHES AMBER** and then switches off there is not enough charge to take a treatment.
    - If the LED does not illuminate, please refer to the troubleshooting section of this manual.
11. Ensure aerosol is coming out of the mouthpiece assembly or mask.
12. **a) If using the mouthpiece,** hold the handset in your hand and place the mouthpiece between your teeth with your lips sealed around it. Breathe normally through your mouth.
    b) If using a mask, hold the handset in your hand and gently press the mask against your face and breathe normally through your mouth.

During use, some aerosol will be emitted from the back of the mouthpiece assembly.

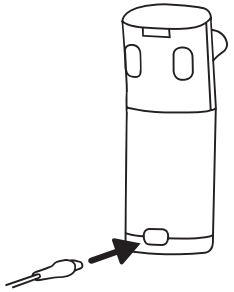


Do not tilt the device in any direction more than 45 degrees during the course of a treatment as this will prevent the nebulizer from completely nebulizing all the medication in the chamber.

13. If you need to take a rest, press the on/off button to stop your treatment. To continue your treatment press the on/off button again.
14. Your treatment is finished when the nebulizer beeps and the LED flashes. The device will turn off automatically.
15. Check the medication chamber for residual medication. If there are more than a few drops remaining, press the on/off button again to continue your treatment.
16. Clean the nebulizer following the cleaning instructions.

Charging the battery

1. Connect the power adapter to the socket on the back of the handset.
2. Plug the other end of the power adapter into the wall outlet.
3. The LED will **PULSE GREEN**.
4. Charge the battery until the LED turns **SOLID GREEN** indicating it is fully charged.
5. Unplug the power adapter from both the handset and the wall outlet. It is recommended to unplug the power adapter once the battery is fully charged to preserve battery life.



Cleaning and maintenance

⚠ Cautions

- **Do not autoclave the mouthpiece assembly or handset.**
- **Do not put any part of the device in a microwave or conventional oven.**
- **Do not immerse the handset in liquid or steam clean.**
- **Never poke or clean the mesh with any sharp objects as this will damage the mesh.**
- **Do not clean the device when in use.**
- **Disconnect device from power supply prior to cleaning.**

Cleaning: home environment and hospital/clinic setting

After each use:

- Pour away residual medication from the medication chamber.
- Press the mouthpiece assembly release button to separate the mouthpiece assembly from the handset.
- Rinse the mouthpiece assembly thoroughly under running tap water.
- Shake off excess water and allow to air dry fully before storing.

Daily cleaning

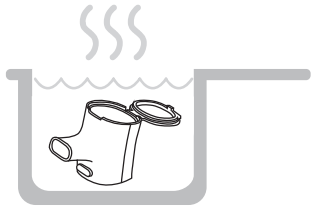
- Wash the mouthpiece assembly by hand in a bowl of warm soapy water (liquid dishwashing soap) for 2 minutes.
- Rinse the mouthpiece assembly thoroughly under running tap water.
- Shake off excess water and allow to air dry fully before storing.

Weekly disinfection

CAUTION: Risk of scalding. Use care around boiling water and in handling hot parts.

- Prior to disinfection, ensure all parts are visibly clean and free from dirt/debris.

  Boil the mouthpiece assembly in water for 10 minutes. Ensure the medication chamber lid is open and there is enough water in the pan to prevent the mouthpiece assembly from touching the bottom or boiling dry. Shake off excess water and allow to air dry fully before storing.



Or

- Immerse the mouthpiece assembly in a disinfectant of the Gluteraldehyde group (testing performed with Korsolex Extra, 4% for 15 minutes). Rinse thoroughly according to manufacturers instructions.

Mask cleaning

- Wipe your handset clean with a clean damp cloth weekly or as needed. Do not use other cleaning methods or solutions.

Handset cleaning

- If using a mask and mask adapter, once a week: agitate for 2 minutes or soak for 10 minutes, in warm soapy water (liquid dishwashing soap), rinse thoroughly under running tap water and air dry fully.
- After each cleaning procedure visually inspect for any remaining dirt/debris, if any remains repeat the procedure. Visually inspect for any moisture before storing.

Maintenance

Mouthpiece assembly can be cleaned (boiled/disinfected) up to 52 times over 12 months.

To keep your InnoSpire Go working at the optimum level you should replace the mouthpiece assembly and mask, if used, every 12 months as this is a consumable part.

LED Indication

LED Indication	What it means
SOLID GREEN	The battery is charged
SOLID AMBER	There is enough charge for at least one more treatment
FLASHES AMBER FIVE TIMES	There is not enough charge to take a treatment
FLASHES GREEN OR AMBER FIVE TIMES	The treatment is finished
PULSES GREEN	The battery is being charged

Troubleshooting

Problems	Solutions
The on button is pressed but nothing happens (no light, no nebulization).	Battery has insufficient charge, follow battery charging instructions. If the problem persists, contact your customer services representative.
LED illuminates on button press but goes off when button released.	Check to ensure that the mouthpiece assembly is attached properly. Make sure that the contacts on the handset are dry and free of debris. Make sure that there is medication loaded in the chamber. Recharge the battery.
When charging the battery, the LED does not pulse or turn on.	Ensure that the power cable is connected to the handset and plugged into the wall outlet or disconnect the power supply and reconnect.
Treatments take longer than usual with the same mouthpiece assembly.	Boil the mouthpiece assembly as per the weekly disinfection instructions.
Device indicates end of treatment but medication remains in medication chamber (more than a few drops).	Ensure nebulizer is held upright during nebulization. If the problem persists, contact your customer services representative.
Device does not indicate end of treatment even though all medication is nebulized.	Contact your customer services representative.

Should the device still not operate properly after checking the unit as indicated above it may have a critical error, contact Philips Customer Service at 1-800-345-6443 or 1-724-387-4000.

Technical specifications

Mains power supply	Input = 100 – 240 V~, 50/60 Hz Output = 5V ⎓, 1.0A
Internal rechargeable battery power supply (lithium polymer)	3.7 Volts nominal, 1200 mAh
Weight	0.29 lbs/111g
Size	2.76" x 1.77" x 5.31" / 7.0cm x 4.5cm x 13.5cm

Class II device internally powered device (double safety insulation)
Type BF device (device with specific protection against electrical hazards)
Ingress Protection rating IP22. (Protected against solid foreign objects of 12.5mm diameter and greater; protected against vertically falling water drops when device titled up to 15°) The InnoSpire Go handset and charger form a Medical Electrical System, in which the charger is not Medical Electrical Equipment. The IP22 rating applies to the InnoSpire Go handset, the charger rating is IPX0.
All components shown in the illustration are applied parts.
Materials: Handset - Polyamide (PA) and Thermoplastic elastomer (TPE),
Mouthpiece Assembly - Polyamide (PA) and Polypropylene (PP)

Certification

Reference to standards
Electric safety standards EN 60601-1
Electromagnetic compatibility according to EN 60601-1-2

Operating conditions

Temperature range of 41° F – 104° F /+ 5 °C to + 40 °C
Humidity range of 15% RH to 93% RH, non-condensing Atmospheric pressure 70 kPa to 106 kPa

Storage and transport conditions

Temperature range of MIN -13° F MAX +158° F / MIN -25° C MAX +70° C
Humidity range of MIN 10% RH –MAX 93% RH Atmospheric pressure 50 kPa to 106 kPa

Replacement parts and optional accessories

Adult mask - large (ages 5 years plus)	1127875
Pediatric mask - medium (ages 2 - 5 years)	1127798
Mask adapter	1125985
Mouthpiece assembly	1128501
Plug adapter	1127651
Carry case	1128576

Technical data EN13544-1

Aerosol output	1.19 mL
Aerosol output rate	0.26 mL/min
Max fill volume	8 ml
Max medication temperature increase at max fill	<10°C above ambient temperature
Noise level	<35dB at 1m
Percentage of fill volume (2.5 mL) as aerosol output (delivered to filter) in one minute	10.2%
Residual volume	0.30 mL

If the device has been stored at the extremes of the storage temperature, please allow at least 1 hour at room temperature before using the device.

This table summarizes the performance with the mouthpiece and with a face mask when nebulizing salbutamol (5 mg/2.5 mL). Values reported are mean and 95% confidence interval. When used with a face mask the performance can be less and you may need to consult your physician about the treatment frequency and length of treatment.

Parameter	InnoSpire Go	InnoSpire Go with adult LiteTouch face mask
Mass median aerodynamic diameter (MMAD)	3.99 µm ± 0.73	4.18 µm ± 0.78
Fine particle fraction <5 µm	64.4% ± 12.2	61.3 ± 12.4
Respirable fraction 1 - 5 µm	62.7% ± 11.6	59.7% ± 12.0
Delivered dose	1.19 mL ± 0.06	0.87 mL ± 0.06
Respirable dose 1 - 5 µm	0.74 mL ± 0.13	0.52 mL ± 0.14

The following particle size specifications were established via performance tests using a seven stage cascade impactor at a flow rate of 15 L/min and 30 L/min equipped with a USP <601> induction port throat. 3 device samples were tested with 3 runs each, for a total of 9 sample points per each drug.

Aerosol was sampled directly from the outlet.

The specifications are listed below with the mean and 95% confidence interval included.

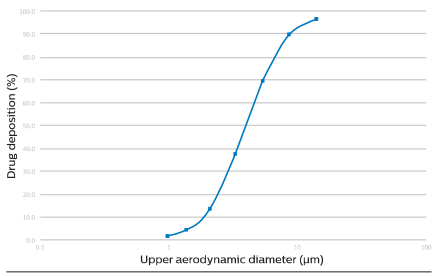
Aerosol specifications

Parameter	Drug	15 L/min extraction flow	30 L/min extraction flow
Mass median aerodynamic diameter (MMAD)	Salbutamol (5 mg/2.5 ml)	3.99 µm ± 0.73	3.90 µm ± 1.04
	Ipratropium bromide (500 µg/2 mL)	3.93 µm ± 0.74	3.87 µm ± 0.90
	Sodium cromoglicate (20 mg/2mL)	4.27 µm ± 0.76	4.02 µm ± 0.91
Geometric standard deviation (GSD)	Salbutamol (5 mg/2.5 ml)	1.82 ± 0.02	2.02 ± 0.11
	Ipratropium bromide (500 µg/2 mL)	1.82 ± 0.03	2.02 ± 0.18
	Sodium cromoglicate (20 mg/2mL)	1.83 ± 0.05	2.00 ± 0.18
Respirable fraction 1 - 5 µm	Salbutamol (5 mg/2.5 ml)	62.7% ± 11.6	56.0% ± 11.9
	Ipratropium bromide (500 µg/2 mL)	63.6% ± 11.8	56.6% ± 9.0
	Sodium cromoglicate (20 mg/2mL)	58.3% ± 11.2	47.9% ± 6.4
Coarse particle fraction >5 µm	Salbutamol (5 mg/2.5 ml)	35.6% ± 12.2	38.9% ± 14.4
	Ipratropium bromide (500 µg/2 mL)	34.7% ± 12.3	38.1% ± 11.4
	Sodium cromoglicate (20 mg/2mL)	40.2% ± 11.6	40.4% ± 11.6
Fine particle fraction <5 µm	Salbutamol (5 mg/2.5 ml)	64.4% ± 12.2	61.1% ± 14.4
	Ipratropium bromide (500 µg/2 mL)	65.3% ± 12.3	61.9% ± 11.4
	Sodium cromoglicate (20 mg/2mL)	59.8% ± 11.6	59.6% ± 11.6
Ultra-fine particle fraction <1 µm	Salbutamol (5 mg/2.5 ml)	1.7% ± 0.6	5.2% ± 2.6
	Ipratropium bromide (500 µg/2 mL)	1.8% ± 0.6	5.4% ± 3.2
	Sodium cromoglicate (20 mg/2mL)	1.5% ± 0.5	11.7% ± 5.8
Respirable dose 1 - 5 µm	Salbutamol (5 mg/2.5 ml)	0.74 mL ± 0.13	0.66 mL ± 0.16
	Ipratropium bromide (500 µg/2 mL)	0.59 mL ± 0.11	0.53 mL ± 0.10
	Sodium cromoglicate (20 mg/2mL)	0.59 mL ± 0.14	0.49 mL ± 0.08
Delivered dose	Salbutamol (5 mg/2.5 ml)	1.19 mL ± 0.06*	
	Ipratropium bromide (500 µg/2 mL)	0.93 mL ± 0.02*	
	Sodium cromoglicate (20 mg/2mL)	1.01 mL ± 0.05*	

* Determined using a simulated breathing pattern (tidal volume = 500 mL, I:E ratio = 1:1, breaths per minute = 15)

Note: Coarse particles (oro-pharyngeal deposition) and ultra-fine particles (exhaled) are not likely to deposit in the patient's airway and thus provide limited clinical benefit.

Cumulative drug deposition – Salbutamol



Performance information provided as required by EN 13544-1:2007 may not apply for medications in suspension or high viscosity form. In such cases information should be sought from the medication supplier.

Performance may vary based on atmospheric pressure depending on altitude above sea level, barometric pressure, and temperature.

Nebulizer performances are based upon testing that utilizes adult ventilatory patterns and are likely to be different from those stated for pediatric (2 years and older) populations.

Electromagnetic information: The InnoSpire Go needs special precautions regarding EMC and needs to be installed and put into service according to the EMC information provided in this document.

Portable and mobile RF communications equipment can affect medical electrical equipment.

The CE mark on the product denotes compliance with all applicable EU Directives. Note that the Notified Body number does not apply to the RoHS (restriction of the use of certain hazardous substances in electrical and electronic equipment) Directive.

Expected service life: Nebulizer handset, battery and mask adapter, 3 years from date of purchase
Mouthpiece assembly, 1 year from date of first use
Masks, 1 year from date of first use

Symbol glossary

- ON (power)
- OFF (power)
- SN Serial number
- Follow instructions for use
- Complies with RTCA/DO-160F section 21, category M
- CAUTION
- Alternating current
- Separate collection
- Atmospheric pressure
- Manufacturer
- Class II internally powered device, double insulated
- Type BF applied parts
- Temperature limitation
- Humidity
- Date of manufacture

IP22 Ingress Protection rating

Warranty

Respironics, Inc warrants the nebulizer handset and battery to be free from defects in materials and workmanship under normal use and operation for a period of 2 years from date of purchase from Respironics, Inc. The warranty is limited to repair or replacement, at Respironics, Inc's sole option, of any such component or equipment claimed to be defective when claim is shown to be bona fide by evaluation by Respironics, Inc. This warranty does not extend to any components or equipment subjected to misuse, improper operation, accidental damage, or unauthorized repairs, and is not extended to charges of, or for, labor repairs. All items returned must be properly packaged and shipped, prepaid, by the product distributor servicing the unit. Respironics, Inc shall not be liable to purchaser or others for loss of use of equipment or for indirect, or incidental or consequential damages that might arise.

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CE 0123

Manufactured for
Respironics Respiratory Drug Delivery (UK) Ltd
Chichester Business Park, City Fields Way
Tangmere, Chichester PO20 2FT UK
www.philips.com/respironics

PN 1128272 R02 OCT 2017

APPENDIX 4. BLOOD VOLUMES TO BE DRAWN

Total Volume of Blood to be Drawn from Each Subject in Part A				
Assessment		**Sample Volume (mL)**	**Number of Samples**	**Total Volume (mL)**
Viral screen (HIV, HBV, HCV)		8.5	1	8.5
Safety	Serum chemistry, CRP, β-hCG[a]	8.5	9	76.5
	Hematology	4.0	9	36.0
	Coagulation	4.5	9	40.5
[redacted] mRNA assay		5.0	6	30.0
[redacted] assay		2.5	6	15.0
CFTR and PEG antibody assay		4.0	6[b]	24.0
CFTR T cell assay		20.0	6[b]	120.0
Total Volume for Study (mL)		-	-	**350.5**

β-hCG=beta-human chorionic gonadotropin; CRP=C-reactive protein; HIV=human immunodeficiency virus; HBV=hepatitis B virus; HCV=hepatitis C virus.
[a] Female subjects only.
[b] Includes the optional blood sample to be collected on the final study day (Day 337 in Part A), if needed for assessment of immune responses to CFTR protein (Section 7.5.2.15).

Total Volume of Blood to be Drawn from Each Subject in Part B				
Assessment		**Sample Volume (mL)**	**Number of Samples**	**Total Volume (mL)**
Viral screen (HIV, HBV, HCV)		8.5	1	8.5
Safety	Serum chemistry, CRP, β-hCG[a]	8.5	11	93.5
	Hematology	4.0	11	44.0
	Coagulation	4.5	11	49.5
Inflammatory markers[c]		1.0	6	6.0
[redacted] mRNA assay		5.0	8	40.0
[redacted] assay		2.5	8	20.0
CFTR and PEG antibody assay		4.0	6[b]	24.0
CFTR T cell assay		20.0	6[b]	120.0
Total Volume for Study (mL)		-	-	**405.5**

β-hCG=beta-human chorionic gonadotropin; CRP=C-reactive protein; HIV=human immunodeficiency virus; HBV=hepatitis B virus; HCV=hepatitis C virus.
[a] Female subjects only.
[b] Includes the optional blood sample to be collected on the final study day (Day 365 in Part B), if needed for assessment of immune responses to CFTR protein (Section 7.5.2.15).
[c] Inflammatory markers to be collected in the 20 mg dose group only.

Total Volume of Blood to be Drawn from Each Subject in Part D				
Assessment		**Sample Volume (mL)**	**Number of Samples**	**Total Volume (mL)**
Viral screen (HIV, HBV, HCV)		8.5	1	8.5
Safety	Serum chemistry, CRP, β-hCG[a]	8.5	11	93.5
	Hematology	4.0	11	44.0
	Coagulation	4.5	11	49.5
Inflammatory markers		1.0	8	8.0
[redacted] mRNA assay		5.0	13	65.0
[redacted] assay		2.5	13	32.5
CFTR and PEG antibody assay		4.0	7[b]	28.0
CFTR T cell assay		20.0	7[b]	140.0
Total Volume for Study (mL)		-	-	**469.0**

β-hCG=beta-human chorionic gonadotropin; CRP=C-reactive protein; HIV=human immunodeficiency virus; HBV=hepatitis B virus; HCV=hepatitis C virus.

[a] Female subjects only.

[b] Includes the optional blood sample to be collected on the final study day (Day 341 in Part D), if needed for assessment of immune responses to CFTR protein (Section 7.5.2.15).