Statistical Analysis Plan

Investigational Product:	ARO-MMP7 Inhalation Solution
Protocol Title:	A Phase 1/2a Study Evaluating the Effects of ARO-MMP7 Inhalation Solution in Healthy Subjects and Patients with Idiopathic Pulmonary Fibrosis
Study Number:	AROMMP7-1001
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Signature Page

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Protocol Number:	AROMMP7-1001
SAP Version/Date:	v1.0 / 12NOV2025

We, the undersigned, have reviewed and approved this Statistical Analysis Plan:

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List of Abbreviations

Abbreviation	Definition
Ae	amount excreted
AE	adverse event
AUC	area under the time-concentration curve
AUC_{0-24}	area under the time-concentration curve from time 0 to 24 hours
AUC_{inf}	area under the time-concentration curve from time 0 extrapolated to infinity
AUC_{0-t}	area under the time-concentration curve from time 0 to the last measurable concentration
AUC_{last}	area under the time-concentration curve from time 0 to the last quantifiable plasma concentration
BALF	bronchoalveolar lavage fluid
BMI	body mass index
CL/F	apparent systemic clearance
CL_r	renal clearance
C_{max}	maximum observed plasma concentration
CRA	Clinical Research Associate
CSR	Clinical Study Report
DLCO	diffusing capacity for carbon monoxide
DSC	Data Safety Committee
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
FEV_1	forced expiratory volume
FIH	first in human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
ICF	informed consent form
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board

Abbreviation	Definition
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MMP	matrix metalloproteinase
MMP7	matrix metalloproteinase 7
mRNA	messenger RNA
NHV	normal healthy volunteer
PD	pharmacodynamic
PI	Principal Investigator
PK	pharmacokinetic
PT	Preferred Term
QTc	corrected QT interval
SAD	single ascending dose
SAP	statistical analysis plan
SOA	Schedule of Assessments
SOC	System Organ Class
$t_{½}$	elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
TIA	transient ischemic attack
ULN	upper limit of normal
VAS	visual analog scale
VZ/F	apparent terminal-phase volume of distribution

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined in the protocol amendment 5 for study AROMMP7-1001 dated 17 January 2025. The scope of this plan includes the planned final analysis to be included in the Clinical Study Report (CSR).

2. STUDY OVERVIEW

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study is:

- To assess the safety and tolerability of ARO-MMP7 in normal healthy volunteers (NHVs) and patients with idiopathic pulmonary fibrosis (IPF)

2.1.2. Secondary Objectives

The secondary objectives of this study are the following:

- To assess the pulmonary safety of ARO-MMP7 in NHVs and patients with IPF using spirometry and diffusion capacity measurements
- To assess the pharmacokinetics (PK) of ARO-MMP7 in NHVs and patients with IPF

2.1.3. Exploratory Objectives

The exploratory objectives of this study are the following:

- To assess the pharmacodynamics (PD) of ARO-MMP7 in NHVs and patients with IPF
- To assess the efficacy of ARO-MMP7 in patients with IPF

2.2. Study Design

2.2.1. Overview

This is a Phase 1/2a, randomized, double-blind, placebo-controlled study in NHVs and patients with IPF. ARO-MMP7 is intended for use in patients with IPF. However, because these patients may have baseline decreased lung function and are frequently on multiple concomitant medications, this study will first evaluate dose levels in an NHV population to generate a baseline understanding of safety in a population with normal airway physiology and limited concomitant medication use prior to evaluating dose levels in patients with IPF. Additionally, NHV cohorts will generate an initial understanding of dose-response, using MMP7 protein concentration as a biomarker of PD effect.

For all cohorts, participants who have signed an Institutional Review Board (IRB)/Ethics Committee (EC) approved informed consent form and met all the protocol eligibility criteria during Screening will be randomized to receive ARO-MMP7 or placebo.

The single ascending dose (SAD) portion of the study includes 5 sequentially enrolled NHV cohorts (A1-A5) treated with escalating single dose levels. For each subject, a single dose at a fixed dose level will be administered once on Day 1. All subjects within a cohort will receive the same dose. Each cohort will contain 8 subjects (6 active:2 placebo). Each single dose cohort will begin with administration of ARO-MMP7 or placebo to 2 sentinel participants (1 ARO-MMP7, 1 placebo). Following the Day 2 evaluation in the sentinel participants, if there are no significant safety concerns based on the Principal Investigator's (PI) judgment, the remaining participants in the cohort will be dosed. Dosing of participants in single-dose cohorts will be staggered by at least 30 minutes such that no 2 participants will be dosed simultaneously.

Following the Day 15 study visit in each of the 2 initial single-dose cohorts (Cohorts A1 and A2), the Data Safety Committee (DSC) will meet to review all cumulative available safety data to vote on dose escalation to the next single-dose NHV cohort (see Study Schema below).

Following the Day 15 study visit in Cohort A3, the DSC will meet to review all cumulative available safety and PD data to vote on:

- Dose escalation to the next single-dose NHV cohort (Cohort A4)
- Initiation of multiple-dose NHV cohorts (Cohorts B1, B2, and B3)

Following the Day 15 study visit in Cohort A4, the DSC will meet to review all cumulative available safety and PD data to vote on:

- Dose escalation to the next single-dose NHV cohort (Cohort A5)*
- Initiation of multiple-dose NHV Cohort B4
- Initiation of IPF cohorts at a dose level up to 116 mg ARO-MMP7

*As this DSC meeting may be held prior to regulatory approval of Cohort A5, opening of Cohort A5 may be allowed subsequent to this meeting based on unanimous written consent of the DSC, without a requirement for an additional meeting. An additional meeting will be held if new safety findings require discussion or should any DSC member request one.

Following the Day 15 study visit in Cohort A5, the DSC will meet to review all cumulative available safety and PD data to vote on:

- Initiation of multiple-dose NHV Cohort B5
- Dose escalation of IPF cohorts up to a dose level of 224 mg ARO-MMP7

Following the Day 15 study visit in Cohort C2, the DSC will meet to review all cumulative available safety and PD data to vote on dose escalation of IPF cohort C3 up to a dose level of 448 mg ARO-MMP7.

At all DSC meetings where PD data are reviewed, the DSC will review acceptable dose levels and intervals to be used in multiple-dose cohorts.

Escalation to the next highest dose level will proceed until the highest planned dose level is completed, or higher dose levels are deemed unnecessary, or the trial is halted prematurely by the PI, DSC, or Sponsor due to safety or other concerns.

Multiple-dose NHV cohorts (B1-B5) are optional and will be enrolled at the discretion of the Sponsor and at the time of Sponsor's choosing (following necessary DSC approval). Cohorts B1-B3 will each contain 6 subjects (4 active:2 placebo); Cohorts B4-B5 will each contain 9 subjects (6 active:3 placebo). For each subject in a multiple-dose NHV cohort, between 2 to 3 total doses at a fixed dose level will be administered. All subjects within a cohort will receive the same dose regimen. The dose level and interval for each cohort will be selected by the Sponsor prior to dosing of the first subject in the cohort, based on review of all available safety and PD data to date. The Sponsor must select a dose level for each cohort that is equal to or less than a dose level that has been previously used in a single-dose NHV cohort and that has been reviewed and approved by the DSC for use in multiple-dose NHV cohorts, and that dose will not be higher than 224 mg ARO-MMP7. The Sponsor will similarly select a dose interval for each multiple-dose NHV cohort based on review of all prior safety and PD data. All subjects in multiple-dose NHV cohorts will receive 1 dose on the Day 1 study visit. Another 1 dose will be given at the Day 15 and/or the Day 29 study visits, dependent upon the dosing interval selected by the Sponsor. The Sponsor must select a total number of doses for these cohorts, between 2 and 3, to be given between Days 1 and 29 at an interval of at least 14 days between doses, in accordance with the dosing regimen used in supporting Good Laboratory Practices (GLP) toxicology studies. No sentinel dosing will occur in these cohorts as all dose levels will have already been tested in single-dose cohorts. Screening for the NHV multiple-dose cohorts can begin prior to DSC approval of cohort opening but dose administration may not proceed until after the DSC has opened the designated cohort.

The IPF patient portion of the study includes 3 cohorts (C1-C3). For each subject in an IPF cohort, between 1 and 3 total doses at a fixed dose level will be administered. All subjects within a cohort will receive the same dose regimen. The dose level and interval for each IPF patient cohort will be selected by the Sponsor prior to dosing of the first patient in the cohort, based on review of all available safety and PD data to date. The Sponsor must select a dose level for each IPF patient cohort that has been reviewed and approved by the DSC for use in IPF cohorts, and that dose will not be higher than the maximum dose of 448 mg ARO-MMP7 (the maximum dose will be 116 mg ARO-MMP7 until DSC review of NHV data from Cohort A5 and DSC approval of further dose escalation). Dose levels in sequential IPF cohorts need not necessarily be ascending but will be adaptive based on data from prior cohorts. The Sponsor will similarly select a dose interval for each IPF patient cohort based on review of all prior safety and PD data. All patients in IPF cohorts will receive 1 dose on the Day 1 study visit. Another dose may be given at the Day 15 and/or the Day 29 study visits, dependent upon the dosing interval selected by the Sponsor. The Sponsor must select a total number of doses for IPF cohorts between 1 to 3, to be given between Days 1 and 29 at an interval of at least 14 days between doses, in accordance with the dosing regimen used in supporting GLP toxicology studies. There will be no intracohort or intrasubject dose escalation. All subjects in each cohort will receive the same dose throughout the study.

The dose regimen to be used in IPF Cohort C1 will be specified and reviewed at the DSC meeting that occurs during Cohort A4. Review of safety and PD data by Sponsor Medical Monitor and Sponsor Pharmacovigilance lead will be documented at time of dose regimen

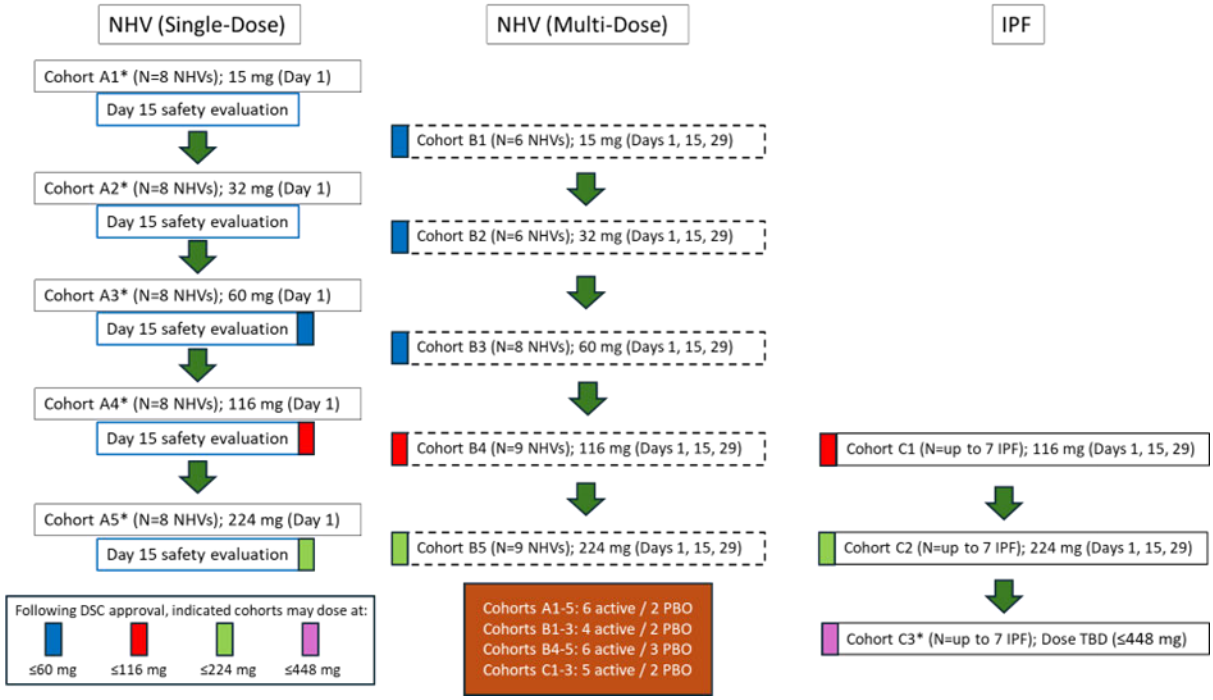
selection for Cohorts C2 and C3. The dose regimen to be used in each IPF cohort will be communicated to clinical sites via a Dose Administration Letter at time of cohort opening.

Each IPF cohort will contain 7 subjects (5 active:2 placebo). Sentinel dosing will be performed in IPF cohort C3 only, as dose levels through 224 mg will have already been tested in single-dose cohorts. Cohort C3 will begin with administration of ARO-MMP7 or placebo to 2 sentinel participants (1 ARO-MMP7, 1 placebo). Following the Day 2 evaluation in the sentinel participants, if there are no significant safety concerns based on the Medical Monitor's judgment, the remaining participants in the cohort will be dosed. IPF Cohort C1 may be opened for accrual at a maximum dose level of 116 mg ARO-MMP7 following review of safety and PD data and approval by the DSC after NHV Cohort A4 has reached study Day 15 (see Study Schema below). Opening of IPF Cohort C1 is not contingent upon prior enrollment of any subjects in NHV multiple-dose cohorts. Dose escalation in subsequent IPF cohorts (ie Cohort C2 or C3) up to 448 mg ARO-MMP7 may be permitted following review of safety and PD data and approval by the DSC after NHV Cohort A5 has reached Study Day 15 (Cohort C2) or NHV Cohort C2 has reached D15 (Cohort C3).

Ad hoc DSC meetings may be arranged as indicated for emergent issues.

For all cohorts, the indicated dose level is the maximum allowable dose for the cohort, but the Sponsor may adjust the dose downward based on available safety and PD data.

Figure 1: Study Schema



Abbreviations: IPF=idiopathic pulmonary fibrosis; NHV=normal healthy volunteer; PBO=placebo; PD=pharmacodynamic; TBD=to be determined.
Note: Cohorts A1 to A5, and C3 (*) use 2 sentinel subjects dosed before the rest of the cohort. Dotted lines indicate optional cohorts.
Dose levels are doses loaded into the nebulizer (nebulizer loaded dose)

Table 1: Schedule of Assessments for Normal Healthy Volunteer Single-Dose Cohorts (Cohorts A1-A4)

Assessment	Day																
	-35 to -2 Screening			-1	1	2	3	8	15	17	18	22	29	43	57	EOS: End of Primary Study Phase / 85 or Early Term	EOS: Follow-up[k]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	F/U #1, #2, etc
Visit Window	-35 to -2 days			±0 days	±0 days			±1 days	±1 days	±3 days	+1 days	±1 days	±2 days	±2 days	±3 days	±3 days	60-day intervals ±7 days
Admit to study site				X													
Informed consent	X																
Eligibility criteria	X				X												
Randomization					X												
Study drug dosing					X												
Demographics	X																
Medical history	X																
Drug screen	X																
Hepatitis/HIV serologies	X																
FSH (in women of postmenopausal age only)	X																

Assessment	Day																
	-35 to -2 Screening			-1	1	2	3	8	15	17	18	22	29	43	57	EOS	
																End of Primary Study Phase / 85 or Early Term	Follow-up[k]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	F/U #1, #2, etc
Visit Window	-35 to -2 days			±0 days	±0 days			±1 days	±1 days	±3 days	+1 days	±1 days	±2 days	±2 days	±3 days	±3 days	60-day intervals ±7 days
Urine cotinine	X																
COVID-19 test[a]	X																
Urine qualitative pregnancy test	X			X												X	X
Body mass index/height/weight[b,c]	X				X									X		X	X
Physical examination (may be symptom directed after Day 1)[b]	X				X	X	X	X	X			X	X	X	X	X	X
ECG[d]	X				X	X	X		X				X			X	
Vital signs (BP, temp, pulse ox, RR, heart rate), perform before other evaluations[b]	X				X	X	X	X	X			X	X	X	X	X	X
Clinical laboratories[b,e]	X				X	X	X	X	X			X	X	X	X	X	X
PK[f]					X	X	X	X									

Assessment	Day																
	-35 to -2 Screening			-1	1	2	3	8	15	17	18	22	29	43	57	EOS	
																End of Primary Study Phase / 85 or Early Term	Follow-up[k]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	F/U #1, #2, etc
Visit Window	-35 to -2 days			±0 days	±0 days			±1 days	±1 days	±3 days	+1 days	±1 days	±2 days	±2 days	±3 days	±3 days	60-day intervals ±7 days
Plasma metabolite ID[f]					X	X	X	X									
Urine collection for excretion and metabolite ID[g]					X	X											
Anti-drug antibodies[b,e]					X							X		X		X	
Spirometry[e,h]	X				X	X	X	X	X			X	X	X	X	X	X
DLCO[b,e,l]					X				X							X	
Chest X-ray (PA and lateral)	X															X	
Serum MMP7[b,e,j]	X				X			X	X			X	X	X	X	X	X
Nasosorption MMP7[b]					X				X				X	X		X	
Bronchoscopy[m]		X								X							
BALF cell count/differential[m]		X								X							
BALF MMP7[m]		X								X							

Assessment	Day																
	-35 to -2 Screening			-1	1	2	3	8	15	17	18	22	29	43	57	EOS	
																End of Primary Study Phase / 85 or Early Term	Follow-up[k]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	F/U #1, #2, etc
Visit Window	-35 to -2 days			±0 days	±0 days			±1 days	±1 days	±3 days	+1 days	±1 days	±2 days	±2 days	±3 days	±3 days	60-day intervals ±7 days
Bronchosorption MMP7[m]		X								X							
Phone call[i]			X								X						
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Abbreviations: BALF=bronchoalveolar lavage fluid; BP=blood pressure; COVID-19=coronavirus disease 2019; DLCO= diffusing capacity for carbon monoxide; ECG=electrocardiogram; EOS=end of study; FSH=follicle stimulating hormone; F/U=follow-up; HIV=human immunodeficiency virus; ID=identification; PA=posteroanterior; PI=Principal Investigator; PK=pharmacokinetic; pulse ox=pulse oximetry; RR=respiratory rate; temp=temperature; Term=termination.

a COVID-19 antigen testing may be performed at any time during Screening window, including Day -1, with timing at the discretion of the PI. COVID-19 testing is the sole Screening assessment that may occur following Screening bronchoscopy (see footnote [m]) should the PI deem such timing appropriate.

b If this assessment is performed on a dosing day, then it must be performed prior to study drug dosing.

c Screening height measurement can be used for all future visits.

d On dosing days, ECGs will be performed predose (-2 hours ±1 hour) and postdose (4 hours ±15 minutes based on start of inhalation) before venipuncture for blood draw if feasible; all ECGs will be performed in triplicate with 3 to 5 minute intervals between each measurement.

e Order of assessments: DLCO, spirometry. Order of other assessments is flexible with the stipulation that indicated assessments must occur prior to dosing or at other specified time points as detailed in footnotes [d], [f], [g], and [h]. Day 1 DLCO may be exempt from this order as indicated in footnote [l].

f Plasma samples for PK analysis and metabolite identification will both be collected at the following time points:

- Day 1: Predose, then postdose (based on start of inhalation) at 0.5, 1, 2, 4, 6, 8, and 12 hours.
- Day 2: 24 hours
- Day 3: 48 hours
- Day 8: 168 hours

The recommended allowance of time windows is ±5 minutes for the 0.5-hour time point and ±10% of nominal time for all other time points. All times are referenced to the beginning of inhalation dosing. If a time window is missed, every effort should be made to collect the PK blood samples with documentation of actual collection times.

g Urine will be collected as a spot predose collection and then as a cumulative collection from 0 to 6 and 6 to 24 hours postdose on Day 1. Subjects must have a spot urine void predose, which must be collected and used as a predose background for analysis. Subjects will be required to attempt to void urine immediately prior to the Day 2 PK collection (24 hours postdose). This void will represent the end of the 6 to 24 hour postdose urine collection period. Metabolite identification will be performed on collected urine samples (pooled analysis).

h On dosing day (Day 1), spirometry measures will be completed predose and postdose at 15 minutes (±10 minutes) and 120 minutes (±15 minutes). On non-dosing days, spirometry measures will only be completed once per visit.

i The phone call during Screening will occur within a window of +1 day following bronchoscopy.

j Samples for serum MMP7 will be collected from all subjects who are screened; however, MMP7 measurement on Screening samples will only be performed for those subjects who are dosed with study drug. For Cohorts A1-A5, the Day 18 phone call will occur within a window of +1 day following the Day 17 bronchoscopy.

k Further follow-up visits are required only if serum MMP7 concentration remains <70% of subject's baseline serum MMP7 concentration at all study visits from Day 22 onward. If follow-up visits are required, the final visit will be the follow-up visit at which serum MMP7 concentration has increased to ≥70% of subject's baseline serum MMP7 concentration.

l Day 1 DLCO may be obtained during the Screening window if clinical site is unable to perform Day 1 DLCO on same day as other Day 1 assessments. If performed during Screening, it may be performed at any time during the window except within 72 hours following bronchoscopy.

m The window for the Screening bronchoscopy is Day -18 to Day -4. Bronchoscopy that is performed during the Screening window will not be performed until all other Screening procedures are complete and subject has otherwise successfully screened into the study; see footnote [a] for potential exception.

Table 2: Schedule of Assessments, Normal Healthy Volunteers, Multiple-Dose Cohorts B4-B5

Assessment	Day																
	-35 to -1 Screening			1	2	15	22	29	30[l]	36	43	44	57	58	71	EOS	
																End of Primary Study Phase / 85 or Early Term	Follow-up[i]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	F/U #1, #2, etc.
Visit Window	-35 to -1 days			±0 days		±1 day	±2 days	±1 day		±2 days	±3 days	+1 days	±3 days	+1 days	±3 days	±5 days	60 -day intervals ±7 days
Informed consent	X																
Eligibility criteria	X			X													
Randomization				X													
Study drug dosing[l]				X		X[l]		X[l]									
Demographics	X																
Medical history	X																
Drug screen	X																
Hepatitis/HIV serologies	X																
FSH (in women of postmenopausal age only)	X																
Urine cotinine	X																
COVID-19 test[a]	X																
Urine qualitative pregnancy test[b,l]	X			X		X[l]		X[l]								X	X
Body mass index/ height and weight[b,c]	X			X				X					X			X	X

Assessment	Day																
	-35 to -1 Screening			1	2	15	22	29	30[l]	36	43	44	57	58	71	EOS	
																End of Primary Study Phase / 85 or Early Term	Follow-up[i]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	F/U #1, #2, etc.
Visit Window	-35 to -1 days			±0 days		±1 day	±2 days	±1 day		±2 days	±3 days	+1 days	±3 days	+1 days	±3 days	±5 days	60 -day intervals ±7 days
Physical examination (may be symptom directed after Day 1)[b]	X			X	X	X	X	X	X[l]	X	X		X		X	X	X
ECG[d]	X			X		X		X			X					X	
Vital signs (BP, temp, pulse ox, RR, heart rate), perform before other evaluations[b]	X			X	X	X	X	X	X[l]	X	X		X		X	X	X
Clinical laboratories[b,e]	X			X		X	X	X		X	X		X		X	X	X
PK[f,l]				X	X	X[l]	X[l]	X[l]	X[l]	X[l]							
Anti-drug antibodies[b,e]				X		X		X			X					X	
Spirometry[e,g]	X			X		X	X	X		X	X		X		X	X	X
DLCO[b,e,k]				X							X					X	
Serum MMP7[b,e,h]	X			X		X	X	X		X	X		X		X	X	X
Nasosorption MMP7[b]				X		X		X			X		X			X	
Chest X-ray (PA and lateral)	X									X						X	
Bronchoscopy[m]		X									X		X				

Assessment	Day																
	-35 to -1 Screening			1	2	15	22	29	30[l]	36	43	44	57	58	71	EOS	
																End of Primary Study Phase / 85 or Early Term	Follow-up[i]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	F/U #1, #2, etc.
Visit Window	-35 to -1 days			±0 days		±1 day	±2 days	±1 day		±2 days	±3 days	+1 days	±3 days	+1 days	±3 days	±5 days	60 -day intervals ±7 days
BALF cell count/differential[m]		X									X		X				
BALF MMP7[m]		X									X		X				
Bronchosorption MMP7[m]		X									X		X				
Phone call[j]			X									X		X			
Adverse events	X	X	X	X	X	X	X	X	X[l]	X	X	X	X	X	X	X	X
Concomitant medications/ therapies	X	X	X	X	X	X	X	X	X[l]	X	X	X	X	X	X	X	X

Abbreviations: BP=blood pressure; COVID-19=coronavirus disease 2019; DLCO=diffusing capacity for carbon monoxide; ECG=electrocardiogram; EOS=end of study; FSH=follicle stimulating hormone; F/U=follow up; HIV=human immunodeficiency virus; ID=identification; PA=posteroanterior; PD=pharmacodynamic; PI=Principal Investigator; PK=pharmacokinetic; pulse ox=pulse oximetry; RR=respiratory rate; temp=temperature; Term=termination.

[a] COVID-19 antigen testing may be performed at any time during Screening window, including Day -1, with timing at the discretion of the PI. COVID-19 testing is the sole Screening assessment that may occur following Screening bronchoscopy (see footnote [m]) should the PI deem such timing appropriate.

[b] If this assessment is performed on a dosing day, then it must be performed prior to study drug dosing.

[c] Screening height measurement can be used for all future visits.

[d] On dosing days, ECGs will be performed predose (-2 hours ±1 hour) and postdose (4 hours ±15 minutes based on start of inhalation) before venipuncture for blood draw if feasible; all ECGs will be performed in triplicate with 3 to 5 minute intervals between each measurement.

[e] Order of assessments: DLCO, spirometry. Order of other assessments is flexible with the stipulation that indicated assessments must occur prior to dosing or at other specified time points. Day 1 DLCO may be exempt from this order as indicated in footnote [k].

[f] A plasma sample for PK analysis will be collected at the following time points:

- Day 1: Predose, then postdose (based on start of inhalation) at 0.5, 1, 2, 4, and 6 hours
- Day 2: 24 hours

- Day 15: Predose, then postdose (based on start of inhalation) at 0.5, 1, 2, 4, and 6 hours
- Day 22: 168 hours
- Day 29: Predose, then postdose (based on start of inhalation) at 0.5, 1, 2, 4, and 6 hours
- Day 30: 24 hours
- Day 36: 168 hours

The recommended allowance of time windows is ±5 minutes for the 0.5 hour time point and ±10% of nominal time for all other time points. All times are referenced to the beginning of inhalation dosing. If a time window is missed, every effort should be made to collect the PK blood samples with documentation of actual collection times.

[g] On dosing days, spirometry measures will be completed predose and postdose at 15 minutes (±10 minutes) and 120 minutes (±15 minutes). On non-dosing days, spirometry measures will only be completed once per visit.

[h] Samples for serum MMP7 will be collected on all subjects who are screened; however, MMP7 measurement on Screening samples will only be performed for those subjects who are dosed with study drug.

[i] Further follow-up visits are required only if serum MMP7 concentration remains <70% of subject's baseline serum MMP7 concentration at all study visits from Day 43 onward. If follow-up visits are required, then the final visit will be the follow-up visit at which serum MMP7 concentration has increased to ≥70% of subject's baseline serum MMP7 concentration.

[j] The phone call during Screening will occur within a window of +1 day following bronchoscopy. For Cohorts B4-B5, the Day 58 phone call will occur within a window of +1 day following the Day 57 bronchoscopy.

[k] Day 1 DLCO may be obtained during the Screening window if clinical site is unable to perform Day 1 DLCO on same day as other Day 1 assessments. If performed during Screening, it may be performed at any time during the window except within 72 hours following bronchoscopy.

[l] Sponsor will determine whether study drug dosing will be performed on Day 15 and/or Day 29 in response to cumulative PD/safety data from NHV single-dose cohorts. This will be determined prior to initiation of the cohort. If study drug dosing is not performed on a given study day (either Day 15 or 29), then urine pregnancy test and PK collections also will not be performed on that study day. Furthermore, Day 22 PK sample collection will only be conducted if dosing is performed on Day 15; similarly, Day 36 PK sample collection will only be conducted if dosing is performed on Day 29. Finally, if study drug dosing is not performed on Day 29, then the Day 30 visit will not be performed.

[m] The window for the Screening bronchoscopy is Day -18 to Day -4. Bronchoscopy that is performed during the Screening window will not be performed until all other Screening procedures are complete and subject has otherwise successfully screened into the study; see (a) for potential exception. During study visits involving bronchoscopy, all other visit assessments are to be performed prior to bronchoscopy, with the exception of blood draws, which may be performed in a ±24-hour window around the bronchoscopy procedure. At the Day 43 visit, spirometry and DLCO must be performed prior to bronchoscopy. At the Day 57 visit, spirometry must be performed prior to bronchoscopy.

Table 3: Schedule of Assessments, Idiopathic Pulmonary Fibrosis Cohorts (C1-C3)

Assessment	Day															
	-35 to -1 Screening			1	2	8[m]	15	22[m]	29	30[o]	36[m]	43	44	57[m]	EOS	
															End of Primary Study Phase / 85 or Early Term	Follow-up[k]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	F/U #1, #2, etc.
Visit Window	-35 to -1 days			±0 days		±2 days	±1 day	±2 days	±1 day		±2 days	±3 days	+1 day	±3 days	±5 days	60-day intervals ±7 days
Informed consent	X															
Eligibility criteria	X			X												
Randomization				X												
Study drug dosing[o]				X			X[o]		X[o]							
Demographics	X															
Medical history	X															
Drug screen	X															
Hepatitis/HIV serologies	X															
FSH (in women of postmenopausal age only)	X															
Urine cotinine	X															
COVID-19 test[a]	X															
Urine qualitative pregnancy test[b,o]	X			X			X[o]		X[o]						X	X

Assessment	Day															
	-35 to -1 Screening			1	2	8[m]	15	22[m]	29	30[o]	36[m]	43	44	57[m]	EOS	
															End of Primary Study Phase / 85 or Early Term	Follow-up[k]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	F/U #1, #2, etc.
Visit Window	-35 to -1 days			±0 days		±2 days	±1 day	±2 days	±1 day		±2 days	±3 days	+1 day	±3 days	±5 days	60-day intervals ±7 days
Body mass index/height and weight[b,c]	X			X					X					X	X	X
Physical examination (may be symptom directed after Day 1)[b,l]	X	X		X	X	X	X	X	X	X[o]	X	X		X	X	X
ECG[d]	X			X			X		X			X			X	
Vital signs (BP, temp, pulse ox, RR, heart rate), perform before other evaluations[b]	X	X		X	X	X	X	X	X	X[o]	X	X		X	X	X
Clinical laboratories[b,e]	X			X		X	X	X	X		X	X		X	X	X
PK[f,o]				X	X	X	X[o]	X[o]	X[o]	X[o]	X[o]					
Anti-drug antibodies[b,e]				X			X		X			X			X	
Spirometry[e,g]	X			X	X	X	X	X	X	X	X	X		X	X	X

Assessment	Day															
	-35 to -1 Screening			1	2	8[m]	15	22[m]	29	30[o]	36[m]	43	44	57[m]	EOS	
															End of Primary Study Phase / 85 or Early Term	Follow-up[k]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	F/U #1, #2, etc.
Visit Window	-35 to -1 days			±0 days		±2 days	±1 day	±2 days	±1 day		±2 days	±3 days	+1 day	±3 days	±5 days	60-day intervals ±7 days
Home spirometry[n]																
DLCO[b,e,p]	X			X								X			X	
Serum MMP7[b,e,h]	X	X		X		X	X	X	X		X	X		X	X	X
Nasosorption MMP7[b]				X			X		X			X			X	
Blood IPF biomarkers[b,e]				X								X			X	
Blood pharmacology biomarkers[b,e]				X								X			X	
Bronchoscopy[i]		X										X				
BALF cell count /differential[i]		X										X				
BALF MMP7[i]		X										X				
Bronchosorption MMP7[i]		X										X				
Serum urea, albumin, and protein		X														
BALF pharmacology biomarkers[i]		X										X				

Assessment	Day															
	-35 to -1 Screening			1	2	8[m]	15	22[m]	29	30[o]	36[m]	43	44	57[m]	EOS	
															End of Primary Study Phase / 85 or Early Term	Follow-up[k]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	F/U #1, #2, etc.
Visit Window	-35 to -1 days			±0 days		±2 days	±1 day	±2 days	±1 day		±2 days	±3 days	+1 day	±3 days	±5 days	60-day intervals ±7 days
Phone call[j]			X										X			
Cough VAS[b]				X					X			X			X	
Adverse events	X	X	X	X	X	X	X	X	X	X[o]	X	X	X	X	X	X
Concomitant medications/ therapies	X	X	X	X	X	X	X	X	X	X[o]	X	X	X	X	X	X

Abbreviations: BALF=bronchoalveolar lavage fluid; BP=blood pressure; DLCO=diffusing capacity for carbon monoxide; ECG=electrocardiogram; EOS=end of study; FSH=follicle stimulating hormone; F/U=follow up; HIV=human immunodeficiency virus; ICF=informed consent form; ID=identification; IEC=Independent Ethics Committee; IPF=idiopathic pulmonary fibrosis; PA=posteroanterior; IRB=Institutional Review Board; NHV=normal healthy volunteer; PA=posteroanterior; PD=pharmacodynamics; PI=Principal Investigator; PK=pharmacokinetic; pulse ox=pulse oximetry; RR=respiratory rate; temp=temperature; Term=termination.

[a] COVID-19 antigen testing may be performed at any time during Screening window, including Day -1, with timing at the discretion of the PI. COVID-19 testing may occur following Screening bronchoscopy (see footnote [i]) should the PI deem such timing appropriate.

[b] If this assessment is performed on a dosing day, then it must be performed prior to study drug dosing.

[c] Screening height measurement can be used for all future visits.

[d] On dosing days, ECGs will be performed predose (-2 hours ±1 hour) and postdose (4 hours ±15 minutes based on start of inhalation) before venipuncture for blood draw if feasible; all ECGs will be performed in triplicate with 3- to 5-minute intervals between each measurement.

[e] Order of assessments: DLCO, spirometry. Order of other assessments is flexible with the stipulation that indicated assessments must occur prior to dosing or at other specified time points.

[f] A plasma sample for PK analysis will be collected at the following time points:

- Day 1: Predose, then postdose (based on start of inhalation) at 0.5, 1, 2, 4, and 6 hours.
- Day 2: 24 hours
- Day 15: Predose, then postdose (based on start of inhalation) at 0.5, 1, 2, 4, and 6 hours.

- Day 29: Predose, then postdose (based on start of inhalation) at 0.5, 1, 2, 4, and 6 hours.
- Day 30: 24 hours
- Days 8, 22, and 36: 168 hours post-dose

The recommended allowance of time windows is ±5 minutes for the 0.5-hour time point and ±10% of nominal time for all other time points. All times are referenced to the beginning of inhalation dosing. If a time window is missed, every effort should be made to collect the PK blood samples with documentation of actual collection times.

[g] On dosing days, spirometry measures will be completed predose and postdose at 120 minutes (±15 minutes). On non-dosing days, spirometry measures will only be completed once per visit.

[h] Samples for serum MMP7 determinations will be collected on all subjects who are screened; however, MMP7 measurement on Screening samples will only be performed for those subjects who are dosed with study drug.

[i] The window for the Screening bronchoscopy is Day -35 to Day -4. Bronchoscopy that is performed during the Screening window will not be performed until all other Screening procedures are complete and subject has otherwise successfully screened into the study, unless the subject is already undergoing a bronchoscopy for reasons independent of this study. See (a) for potential exception. During study visits involving bronchoscopy, all other visit assessments are to be performed prior to bronchoscopy, with the exception of blood draws, which may be performed in a ±24-hour window around the bronchoscopy procedure.

[j] The phone call during Screening will occur within a window of +1 day following bronchoscopy. For Cohorts C1-C3, the Day 44 phone call will occur within a window of +1 day following the Day 43 bronchoscopy

[k] Further follow-up visits are required only if serum MMP7 concentration remains <70% of subject's baseline serum MMP7 concentration at all study visits from Day 43 onward. If follow-up visits are required, then the final visit will be the follow-up visit at which serum MMP7 concentration has increased to ≥70% of subject's baseline serum MMP7 concentration.

[l] Physical examination on bronchoscopy visits (Visits #2 and #12) may be limited in scope to an examination that the PI deems clinically indicated prior to bronchoscopy.

[m] These study visits may optionally be conducted as either in-clinic visits or home health visits. Use of home health services is permissible contingent upon compliance with local laws and regulations and the capability of the PI to adequately monitor subject safety. In cases where home health services are to be used, this approach, and any specific risks associated with it, must be clearly outlined in the IEC/IRB-approved ICF. The spirometry assessment during a home health visit will be obtained using a portable spirometer (see footnote [n]).

[n] Prior to the end of Screening, subjects expected to complete randomization will be provided with a spirometer for use at home. They will be asked to perform home spirometry daily at least 3 times prior to Day 1 and then daily from Day 1 through EOS. Subjects will be prompted to perform home spirometry during any home health visit that occurs.

[o] Sponsor will determine whether IPF cohort study drug dosing will be performed on Day 15 and/or Day 29 in response to cumulative PD/safety data from NHV cohorts. This will be determined prior to initiation of the cohort. If study drug dosing is not performed on a given study day (either Day 15 or 29), then urine pregnancy test and PK collections also will not be performed on that study day. Furthermore, Day 22 PK collection will only be obtained if dosing is performed on Day 15; similarly, Day 36 PK collection will only be obtained if dosing is performed on Day 29. Finally, if study drug dosing is not performed on Day 29, then the Day 30 visit will not be performed.

[p] If site is unable to perform pre-dose DLCO on Day 1 (eg, due to logistical considerations), then Day 1 DLCO assessment may be performed prior to Day 1 (window: Day -4 to Day -1). In such a case, there must be at least 4 days between the Screening bronchoscopy and the Day 1 DLCO assessment.

2.2.2. Randomization and Blinding

2.2.2.1. Randomization

All potential study subjects who sign an informed consent form (ICF) at Screening will receive a unique identifier (ie, a Screening number). For study subjects who are deemed eligible, this unique screening number will become the subject's permanent study ID number.

Eligible subjects will be allocated a unique randomization number in accordance with the randomization schedule. Treatments will be administered per the randomized sequence generated by interactive web response system (IWRS). The randomization numbers will be grouped in blocks. In NHV Cohorts A1 to A5 and IPF Cohort C3, the first 2 healthy volunteers (sentinels) will be randomized separately to 1 active and 1 placebo.

The randomization schedules and randomization number assignments will be maintained electronically in the IWRS. The personnel involved in the dispensing of IPs will be accountable for ensuring compliance to randomization schedules. The nonblinded clinical research associate (CRA) will have IWRS access to verify the subject's treatment arm (ie, ARO-MMP7 or placebo) and will compare it against the dispensing log to verify the correct study drug assignment.

2.2.2.2. Blinding

The principal investigator (PI) and study participants will remain blinded to treatment allocation of subjects until database lock. Selected Sponsor members will be unblinded to treatment allocation of subjects throughout the entire study.

Blinding of active treatment/placebo assignment is essential to the integrity of this clinical study. It is expected that in most cases, adverse events (AEs) can be properly managed without the need for unblinding. However, in the event of a medical emergency in which knowledge of an individual subject's assignment is considered critical to the subject's wellbeing and management, the PI or documented, designated treating physician or the Sponsor Medical Monitor can unblind the treatment assignment. If the situation is not an immediate emergency, the PI should contact the responsible Medical Monitor to discuss the subject and circumstances requiring the unblinding. The blind will be broken only for the specific subject under discussion. The Study Medical Monitor should be informed promptly. In addition, disclosure of treatment allocation information to DSC members may occur, if necessary, to determine whether a stopping rule has been met and, if so, for subsequent DSC discussion regarding the conduct of the trial.

If the PI considers an AE to be of such severity as to require immediate specific knowledge of the identity and dose of the relevant product, unblinding will be completed via IWRS. The "Medical Emergency Unblinding" transaction in the IWRS is only accessible to the designated unblinded pharmacist, PI, and sub-Investigator. The Medical Monitor should be informed promptly.

If a subject requires emergency unblinding (with or without a discussion between the PI and the Medical Monitor preceding the unblinding), the PI may also be required to complete a "Drug Safety Unblinding Request/Notification Form" to document the medical rationale necessitating the unblinding. This form is then forwarded to the local Medical Monitor.

2.3. Study Endpoints

2.3.1. Primary Endpoints

The primary endpoint of this study is:

- The incidence and frequency of treatment-emergent adverse events (TEAEs) over time through end of study (EOS) in NHVs and patients with IPF

2.3.2. Secondary Endpoints

The secondary endpoints of this study are the following:

- Change from baseline over time through EOS in forced expiratory volume (FEV1) in NHVs and patients with IPF as a safety assessment
- Change from baseline over time through EOS in forced vital capacity (FVC) in NHVs and patients with IPF as a safety assessment
- Change from baseline over time through EOS in diffusing capacity for carbon monoxide (DLCO) in NHVs and patients with IPF as a safety assessment
- Plasma pharmacokinetic (PK) parameters of ARO-MMP7 in NHVs and patients with IPF
- Urinary excretion of ARO-MMP7 in healthy volunteers

2.3.3. Exploratory Endpoints

The exploratory endpoints of this study are the following:

- Change from baseline over time through EOS in MMP7 protein concentration from serum samples in NHVs and patients with IPF as a PD assessment
- Change from baseline over time through EOS in MMP7 protein concentration from nasal fluid samples collected by nasosorption in NHVs and patients with IPF as a PD assessment
- Change from baseline to follow-up bronchoscopy in MMP7 protein concentration from bronchoalveolar lavage fluid (BALF) samples in NHVs and patients with IPF as a PD assessment
- Change from baseline to follow-up bronchoscopy in MMP7 protein concentration from airway fluid samples collected by bronchosorption in NHVs and patients with IPF as a PD assessment
- Change from baseline to Day 43 in a MMP7 pharmacology biomarker panel from BALF samples in patients with IPF as a PD assessment
- Change from baseline over time through EOS in a MMP7 pharmacology biomarker panel from blood samples in patients with IPF as a PD assessment
- Change from baseline over time through EOS in IPF biomarkers from blood samples in patients with IPF as a PD assessment

- Change from baseline to follow-up bronchoscopy in BALF cell count and differential in NHVs and patients with IPF as a safety assessment
- Change from baseline over time through EOS in FEV1 measured by home spirometry in patients with IPF as a safety assessment
- Change from baseline over time through EOS in FVC measured by home spirometry in patients with IPF as both a safety and an efficacy assessment
- Change from baseline over time through EOS in chest X-ray findings in NHVs as a safety assessment
- Change from baseline over time through EOS in cough visual analog scale (VAS) in IPF patients as a safety assessment
- Change from baseline over time through EOS in FVC in patients with IPF as an efficacy assessment
- Change from baseline over time through EOS in DLCO in patients with IPF as an efficacy assessment
- Identification of ARO-MMP7 metabolites in plasma and urine after a single dose of study drug in NHVs
- Incidence and titer of anti-drug antibodies over time through EOS (if criteria are met; see Section 3.8)

3. STATISTICAL METHODOLOGY

3.1. General Considerations

3.1.1. Summary Statistics

Descriptive statistics will be presented for all analyses unless otherwise specified. For continuous variables, data will be presented as number (n), mean, median, standard deviation, minimum, and maximum. Discrete variables will be presented as frequencies and proportions or percent. Data will be analyzed by regimen and population (SAD NHV, MAD NHV and patients with IPF). Within each regimen and population, data will be summarized by cohort. Data summarized in tables and figures will also be presented in subject listings. For each regimen and population (SAD NHV, MAD NHV, patients with IPF), subjects who receive placebo will be pooled and subjects who receive IP will be pooled.

3.1.2. Baseline and Study Day

Day 1

Day 1 is defined as the date of first administration of study drug. If the date of first study drug administration is missing, date of randomization will be used as Day 1. Study day is calculated relative to the date of Day 1 as follows:

- For any events on or after the first administration of the study drug, study day is calculated as: event date – date of first administration of study drug + 1.

- For any events before the first administration date, study day is calculated as: event date – date of first administration of study drug. As such, one day before the first administration date is study day -1.

Baseline

Unless otherwise specified, "Baseline" is defined as the last observed value of the parameter of interest prior to the first administration of study treatment (this includes unscheduled visits).

Change from baseline is calculated as post-baseline values minus baseline values. Percentage change from baseline is calculated as ratio of change from baseline and baseline expressed as a percentage.

Percent change from baseline = ((post-baseline – baseline)/baseline) *100%

3.1.3. Analysis Visits

Scheduled visits will be assigned to analysis visits as recorded on the electronic case report form (eCRF). Where applicable, for assessments that may continue to be collected at follow-up visits beyond Day 85 and per the Schedule of Assessments in the Protocol, an "End of Study" visit will be derived.

3.1.4. Hypothesis Testing

For this FIH exploratory study, no hypothesis is considered.

3.2. Analysis Sets

The following analysis sets are defined:

3.2.1. Full Analysis Set

All subjects who randomized to study. The Full Analysis Set will be used for analyzing efficacy endpoints.

3.2.2. Safety Analysis Set

All subjects who receive at least 1 dose of IP. The Safety Analysis Set will be used for safety analyses. Subjects will be included in the analyses according to the treatment they received.

3.2.3. PK Analysis Set

All subjects who receive at least 1 dose of IP and have sufficient plasma concentration data to facilitate determination of PK parameters. Subjects with major protocol violations will be assessed on a subject-by-subject basis for inclusion in the PK Analysis Set. The PK Analysis Set will be used for PK analyses.

3.3. Covariates and Subgroups

The protocol does not define any formal subgroup analyses. Any additional subgroups of interest will be identified in the final CSR as post hoc analyses.

3.4. Subject Data and Study Conduct

3.4.1. Subject Disposition

Counts and percentages of subjects who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized will be summarized in total based on all screened subjects.

Counts and percentages of subjects who were randomized, discontinued early from the treatment, discontinued early from the study, completed the treatment and completed the study will be summarized by treatment and in total based on the Safety Analysis Set. Reasons for early discontinuation will also be summarized.

Counts and percentages of subjects in each analysis set will be summarized by treatment and in total based on the Safety Analysis Set.

3.4.2. Protocol Deviations

A subject data listing of protocol deviations will be provided by subject.

3.4.3. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics or counts and percentages of subjects as appropriate by treatment and in total based on the Safety Analysis Set.

The following demographic and baseline characteristics will be summarized:

- Age (years)
- Sex at Birth
- Race
- Ethnicity
- Height (cm)
- Weight (kg)
- Body mass index (BMI) (kg/m^2)
- Serum MMP7 protein concentration (ng/L)
- BALF MMP7 protein concentration (ng/L)

A subject data listing containing demographic and baseline characteristics will be provided.

For patients with IPF, the following baseline disease characteristics will be summarized:

- Age of patient when idiopathic pulmonary fibrosis diagnosis made (Years)
- Surgical lung biopsy contribute to patient's idiopathic pulmonary fibrosis diagnosis (Yes/No)
- Use supplemental oxygen (Yes/No)

- Number of total idiopathic pulmonary fibrosis exacerbations in the previous year
- Number of total idiopathic pulmonary fibrosis exacerbations in the previous year that resulted in hospitalization
- On nintedanib or pirfenidone at baseline (Yes/No)

A subject data listing containing baseline disease characteristics will be provided.

3.4.4. Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.0. Counts and percentages of subjects with medical history by system organ class and preferred term will be summarized by treatment and in total based on the Safety Analysis Set.

A subject data listing containing medical history will be provided.

3.4.5. Concomitant Medications

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary version B3 Global March 2022. For summary purposes, medications will be considered prior medications if they were taken prior to the time the subject provides informed consent (at Screening). Medications will be considered concomitant medications if they were taken at any time from the date of signature of informed consent until EOS (i.e. started prior to the informed consent signature date and were ongoing or started after the informed consent signature date). A medication can be considered both prior and concomitant.

If a medication has incomplete start or stop dates, dates will be imputed to determine whether a medication should be considered prior and concomitant. If a medication start date is incomplete, the first day of the month will be imputed for missing day and January will be imputed for missing month. Incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of subjects taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the Safety Analysis Set.

A subject data listing containing prior and concomitant medications and concomitant procedures will be provided.

3.4.6. Investigational Product Exposure

Investigational Product exposure will be summarized descriptively based on the Safety Analysis Set for the following categories:

- Total number of IP administrations, excluding interruptions (category): 1 Dose, 2 Doses, 3 Doses
- Duration of IP exposure (in days) during the Treatment Period (continuous), calculated as: [(date of Last IP administration +14) – date of first IP administration] + 1

Note that the IP exposure categories above do not take inhalation interruptions into account.

A subject data listing for IP exposure will be provided.

3.5. Safety Analyses

Safety data will be summarized by actual treatment received based on the Safety Analysis Set.

3.5.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) version 25.0 or later will be used to code all events categorized as adverse events to a system organ class and a preferred term.

AEs will be classified as treatment emergent based on the TEAE definition, any adverse event occurring between the date of first IP administration and the end of study, or a pre-existing condition exacerbated following IP administration. For AEs starting on the same date as the first IP administration, the field on the adverse events CRF page "Did Adverse Event occur prior to the 1st dose?" will determine the TEAE classification (a result of "No" will indicate the AE is treatment emergent). Derived TEAE classifications will be used for all summaries.

If an adverse event has an incomplete start date, dates will be imputed to determine whether the adverse event should be classified as treatment emergent. Imputed dates will not be earlier than the subject's date of first IP administration. If all year, month, and day are missing, the AE start date will be imputed to the subject's date of first IP administration. If AE start year is available but month and day are missing the AE start date will be imputed to the 1st of January of the AE start year. If AE start year and month are available but day is missing the AE start date will be imputed to the 1st day of the AE start month.

In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified conservatively, i.e., as treatment emergent. Incomplete adverse event end dates will not be imputed.

An overall summary of AEs will be provided containing total frequency of as well as number and percentage (incidence) of subjects reporting at least one: TEAEs, treatment emergent serious adverse events (TESAEs), related TEAEs, related TESAEs, TEAEs leading to study discontinuation, TEAEs leading to drug withdrawal, and TEAEs resulting in death. The summary will also include TEAEs by maximum severity (total frequency will not be provided for this category). In all summaries, when calculating the incidence of adverse events, each subject will only be counted once.

The incidence and frequency of adverse events will be tabulated by System Organ Class (SOC) and Preferred Term (PT) in decreasing order of the overall frequency for the following categories:

- TEAEs
- TEAEs by maximum severity (mild, moderate, severe)
- TESAEs
- Deaths
- Treatment-related TEAEs
- Treatment-related TESAEs

- TEAEs leading to study discontinuation
- TEAEs leading to drug withdrawal

Additionally, the incidence and frequency of TEAEs will be summarized by PT in decreasing order of the overall frequency. When summarizing subject incidence of adverse events, only the worst grade of each preferred term will be counted so each preferred term will only be counted once per subject.

A subject data listing containing all adverse events data and a subject data listing containing serious adverse events will be provided.

3.5.2. Spirometry

In NHVs, spirometry serves as a safety assessment only. In patients with IPF, spirometry serves primarily as an assessment of safety but also provides exploratory insight into efficacy. In patients with IPF, efficacy analyses will be performed on the first spirometry assessment of a study visit (via comparison with baseline spirometry results). Any subsequent spirometry measures obtained during the study visit (i.e., after dosing with study drug) serve primarily safety purposes.

Spirometry will be performed both in-clinic (NHVs and IPF patients) and at-home (IPF patients).

Spirometry maneuvers will be repeated to achieve 3 acceptable FEV1 and FVC measurements. An upper limit of 8 maneuvers should be performed to attempt to produce 3 acceptable measurements. Assessments will be transmitted to a central vendor for quality review (over-reader) where the maneuvers and overall Spirometry session will be graded as Accepted (Passed QA) or Rejected (Failed QA). The best FEV1 and FVC from a given spirometry assessment will be used for analysis and sessions that are graded as Rejected will be excluded. As a sensitivity analysis, the same analysis will be repeated and sessions that are graded as Rejected will be included (including during the baseline definition). Subjects who did not refrain from vigorous exercise for 1 hour prior to spirometry measurements will be excluded from analysis, using the question from EDC data “Did subject refrain from vigorous exercise for at least 1 hour prior to spirometry measurements?”.

For in-clinic spirometry, the actual value and derived change from baseline to each protocol-specified scheduled visit/time point will be summarized for spirometry tests in both NHVs and IPF patients including: forced expiratory volume (FEV1), forced vital capacity (FVC), predicted FEV1 (FEV1P), percent predicted FEV1 (FEV1PP), predicted FVC (FVCP), percent predicted FVC (FVCPP), FEV1/FVC ratio (FEV1FVC), predicted FEV1/FVC ratio (FEV1FVCP), and percent predicted FEV1/FVC ratio (FEV1FVCPP).

Shift tables from baseline to worst postbaseline value will be generated for in-clinic spirometry tests.

For at-home spirometry, the actual value and derived change from baseline to each protocol-specified scheduled visit/time point will be summarized for the above tests in IPF patients.

Plots of mean observed value, absolute change from Baseline, and percent change from Baseline of FEV1 and FVC will be provided.

Plots of mean observed value and absolute change from Baseline of FEV1PP, FVCPP, and FEV1/FVC will be provided.

Listings for at-home spirometry results will be generated for IPF patients.

A subject data listing containing all spirometry data will be provided.

3.5.3. Diffusing Capacity for Carbon Monoxide (DLCO)

In NHVs, DLCO serves as a safety assessment only. In patients with IPF, DLCO serves primarily as an assessment of safety, but also provides exploratory insight into efficacy. DLCO data will be transmitted to a central vendor for quality review. The session will be graded as Accepted (Passed QA) or Rejected (Failed QA). The DLCO sessions that are graded as Rejected will be excluded from analysis. As a sensitivity analysis, the same analysis will be repeated and sessions that are graded as Rejected will be included.

The actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for DLCO tests including: Diffusion Capacity (DLCO), predicted DLCO (DLCOP), percent predicted DLCO (DLCOPP), predicted DLCO corrected for hemoglobin (DLCOHCP), percent predicted DLCO corrected for hemoglobin (DLCOHCPP).

Plots of mean observed value, absolute change from Baseline, and percent change of DLCO will be provided.

A subject data listing containing all DLCO data will be provided.

3.5.4. Laboratory Tests Results

Clinical laboratory values will be expressed using International System of Units (SI) units.

The actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for each clinical laboratory test from the clinical lab assessments: hematology, blood chemistry, coagulation, and urinalysis.

The incidence of lab abnormalities will be summarized by visit/time point for clinical lab tests from hematology and blood chemistry lab assessments. Results will be classified as “Below” when below the lower limit of normal (< ULN), “Above” when above the upper limit of normal (> ULN), and “Within” when within the normal limits (Normal), as applicable. Unscheduled assessments will be included in abnormality summary tables.

Shift tables from baseline to worst postbaseline value will be generated for clinical lab tests from hematology and blood chemistry assessments. Unscheduled assessments will be included in shift tables.

Subject data listings will be provided for the following assessments. As applicable, listings will include abnormality classifications: “Below” when classified as below the lower limit of normal, “Above” when above the upper limit of normal, and “Within” when within the normal limits.

- Hematology data
- Blood chemistry data
- Coagulation data

- Urinalysis data
- Virus serology data
- COVID-19 testing data
- Drug screen data
- Urine Cotinine data
- Pregnancy, including follicle-stimulating hormone (FSH), data
- Other clinical laboratory data

3.5.5. Cough Visual Analog Scale (VAS)

The cough VAS consists of a line 100 mm in length. The patient will be asked to mark their cough severity along the line, with severity ranging from 0 mm (no cough) to 100 mm (worst cough). The actual value and derived change from baseline to each protocol-specified scheduled visit/time point will be summarized for cough VAS in IPF patients.

A subject data listing containing all cough VAS data will be provided.

3.5.6. Vital Signs

The actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for each vital sign test including Respiration Rate, Temperature, Pulse Rate, Oxygen Saturation, Systolic Blood Pressure, and Diastolic Blood Pressure.

A subject data listing containing all vital signs data, including vital signs clinical significance, will be provided.

3.5.7. 12-Lead Electrocardiograms (ECG)

ECG qualitative results will be summarized descriptively, including the number and percent of subjects with normal, abnormal, and clinically significant abnormal results by visit/time point and triplicate.

The actual value and derived change from Baseline to each protocol-specified scheduled visit/time point will be summarized for ECG quantitative results including Heart Rate (beats/min), PR Interval (msec), RR Interval (msec), QRS Duration (msec), QT Interval (msec), and QTcF (msec). When assessments are performed in triplicate, the average of all available results at each visit/time point will be used for analysis.

An outlier analysis will be performed for QT interval corrected for heart rate using Fridericia's formula (QTcF).

The analysis will include all individual original, repeat, and unscheduled postdose values.

The maximum postdose values will be summarized by treatment according to the following categories:

- >450 ms

- >480 ms
- >500 ms

The maximum increases from baseline will be summarized by treatment according to the following categories:

- >30 ms
- >60 ms

A subject data listing containing all ECG data will be provided.

3.5.8. Physical Examinations

Physical Examinations qualitative results will be summarized descriptively by visit/time point.

A subject data listing containing all Physical Examinations data will be provided.

3.5.9. Chest X-rays

Chest X-ray qualitative results will be summarized descriptively by visit/time point for NHVs.

A subject data listing containing all Chest X-ray data will be provided.

3.5.10. BALF Cell Count and Differential

BALF cell count and differential will be collected from all bronchoscopies performed in every cohort. The provided average of two readers findings, which may include the initial two independent readers or the third adjudication reader when necessary and as determined by the central vendor, will be used for analysis. Actual value and derived change from baseline to each protocol-specified scheduled visit/time point will be summarized for BALF cell count and differentials.

Plots of mean observed and mean change from baseline BALF cell count and differentials will be provided. Plots displaying individual subject results will also be provided.

A subject data listing containing all BALF cell count and differentials will be provided.

3.5.11. IPF Exacerbation Assessments

A subject data listing containing IPF Exacerbation Assessment data will be provided.

3.6. Pharmacodynamic (PD) Analyses

Pharmacodynamic analyses will be performed based on the Full Analysis Set, unless otherwise stated. Data will be analyzed by cohort. Placebo subjects and subjects receiving active drug will be pooled separately.

Descriptive statistics calculations will be performed by scheduled study visit and the derived and percentage change from baseline will be provided for the following measures of PD activity:

- MMP7 protein concentration for NHVs and patients with IPF from serum samples, nasal fluid samples collected by sputum, nasosorption, bronchoalveolar lavage fluid (BALF) samples, and airway fluid samples collected by bronchosorption.
- MMP7 pharmacology biomarker panel for patients with IPF from BALF and blood samples.
- IPF disease state biomarkers from blood samples in patients with IPF.

Plots mean observed value, absolute change from Baseline, and percent change from Baseline will be provided. Plots displaying individual subject results will also be provided.

Subject data listings for measures of PD activity will be provided.

3.7. Efficacy Analyses

Efficacy analyses will be performed based on the Full Analysis Set, unless otherwise stated. Efficacy data for patients with IPF will be analyzed by cohort, placebo subjects and subjects receiving active drug will be pooled separately.

In patients with IPF, efficacy analyses will be performed on the first spirometry assessment of a study visit (via comparison with baseline spirometry results).

Descriptive statistics calculations will be performed by scheduled study visit and the derived and percentage change from baseline will be provided for the following measures of efficacy:

- FVC in patients with IPF. These in-clinic spirometry tests will be included in analysis: forced vital capacity (FVC), predicted FVC (FVCP), percent predicted FVC (FVCPP)

Same as safety analysis, FVC sessions that are graded as Rejected will be excluded. As a sensitivity analysis, the same analysis will be repeated and sessions that are graded as Rejected will be included (including during the baseline definition). Subjects who did not refrain from vigorous exercise for 1 hour prior to spirometry measurements will be excluded from analysis, using the question from EDC data “Did subject refrain from vigorous exercise for at least 1 hour prior to spirometry measurements?”.

Plots mean observed value, absolute change from Baseline, and percent change from Baseline will be provided.

3.8. Immunogenicity Analysis

Preliminary PK analysis suggests PK is not altered over time following repeated dosing. There is no evidence of altered PD or immune-mediated adverse events. The low immunogenicity risk associated with ARO-MMP7 supports the collect-and-hold immunogenicity testing strategy throughout early phases of clinical program. As such, ADA testing and analysis will be deferred.

3.9. Pharmacokinetic (PK) Analysis

Plasma ARO-MMP7 concentrations from healthy volunteers and patients with IPF will be analyzed using noncompartmental analysis in Phoenix WinNonlin (version 8.5 or higher). A standalone report (PK Report) detailing PK parameter estimation and reporting will be provided for inclusion in the clinical study report (CSR).

The following plasma PK parameters will be calculated as applicable for subjects in the single-dose cohorts (Cohorts A1-A5):

- Maximum observed plasma concentration (C_{max})
- AUC from time 0 to 24 hours (AUC_{0-24})
- AUC from time 0 to the last quantifiable plasma concentration (AUC_{last})
- AUC from time 0 extrapolated to infinity (AUC_{inf})
- Elimination half-life ($t_{½}$)
- Apparent systemic clearance (CL/F)
- Apparent terminal-phase volume of distribution (Vz/F)

The following plasma PK parameters will be calculated as applicable for subjects in the multiple-dose cohorts (Cohorts B1-B5, and C1-C3):

- Maximum observed plasma concentration (C_{max})
- AUC from time 0 to the last quantifiable plasma concentration (AUC_{last})

The following urine PK parameters will be calculated as applicable for subjects in the single-dose cohorts (Cohorts A1-A5):

- Recovery of unchanged drug in urine over 0 to 24 hours (amount excreted; Ae)
- Fraction of dose of unchanged drug in urine over 0 to 24 hours (fraction excreted; fe)
- Renal clearance (CL_R)

Additional PK parameters may be estimated as appropriate. Urine and plasma ARO-MMP7 concentrations will be listed, summarized, and plotted as appropriate. Urine and plasma ARO-MMP7 PK parameters will be listed and summarized descriptively. The plasma PK parameters (C_{max} and AUC) will be analyzed for dose proportionality. Plasma and urine metabolite abundances will be analyzed as appropriate.

4. SAMPLE SIZE DETERMINATION

No formal sample size calculations were performed to determine cohort sizes in this Phase 1/2a study aimed primarily at evaluating the safety and tolerability of ARO-MMP7. When the probability of observing a TEAE from a single subject who received active drug is 30%, the chance of observing at least 1 TEAE is higher than 75% among 4 dosed subjects, 83% among 5 dosed subjects and 88% among 6 dosed subjects.

5. PLANNED ANALYSES

5.1. Data Safety Committee (DSC) and Early Stopping Guides

A Data Safety Committee meeting will occur during each single-dose cohort to formally review aggregate safety and PD data through the Day 15 study visit of the cohort. The DSC will vote to escalate to single-dose cohorts at higher dose levels as well as to open optional NHV multiple-dose cohorts. The final planned DSC meeting during Cohort A4 will vote to open IPF cohorts. The DSC may also meet as needed to review and discuss any safety issues that may arise.

The DSC will consist of at least 1 study Investigator, Sponsor Medical Monitor, Sponsor Pharmacovigilance Lead, and an independent physician experienced in pulmonary drug development and/or early-stage clinical trials.

5.2. Interim Analysis

For all NHV cohorts, interim analyses may occur after completion of each NHV cohort (ie, after all subjects within a cohort complete the study or discontinue early). For IPF patient cohorts, interim analyses may occur when all subjects within each cohort complete their Day 85 visit (or discontinue early). Additional exploratory analyses may be done prior to completion of each cohort. Unblinded tables, listings, and figures from interim analyses will be kept in a secure location. Only designated unblinded personnel, documented in the Data Access Plan, will have access to individual treatment assignment before database lock.

5.3. Final Analysis

The Final Analysis will be performed on all unblinded safety and efficacy data once all subjects complete the last visit or early termination, whichever is earlier, and after database lock. Data will be cleaned, and all queries will be addressed before database lock.

6. CHANGE FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

As of this date, there have been no changes between the protocol-defined statistical analyses and those presented in this statistical plan. Of note, ADA testing and analysis will be deferred according to the collect-and-hold immunogenicity testing strategy.

7. PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. Additional programming specifications are provided in a companion document.