Clinical Study Protocol

Protocol No.: INS018-055-003

Official Title of Study: A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of INS018_055 Administered Orally to Subjects With Idiopathic Pulmonary Fibrosis (IPF)

NCT Number: NCT05938920

CLINICAL STUDY PROTOCOL

A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of INS018_055 Administered Orally to Subjects with Idiopathic Pulmonary Fibrosis (IPF)

PROTOCOL NO. INS018-055-003

Sponsor:	InSilico Medicine Hong Kong Limited Unit 310, F3, Building 8W, Phase 2, Hong Kong Science Park, Pak Shek Kok, New Territories, Hong Kong
Sponsor Contact:	[redacted] Telephone: [redacted]
Medical Monitor:	[redacted] Labcorp Clinical Development s.r.l. Avenue du Bourget 50 1130 Brussels Belgium Telephone: [redacted]
Version of Protocol:	4.0 (Amendment Version: 3.0)
Date of Protocol:	02Feb2024

CONFIDENTIAL

The study will be conducted according to the International Council for Harmonization Guideline E6(R2): Good Clinical Practice.

Sponsor Signature Page

PROTOCOL TITLE: A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of INS018_055 Administered Orally to Subjects with Idiopathic Pulmonary Fibrosis (IPF)

PROTOCOL NUMBER: INS018-055-003

[redacted]

2/28/2024

Date

Investigator Protocol Agreement Page

I have carefully read this study protocol and agree that it contains all necessary information required to conduct this study. I agree to conduct the study according to this protocol (including any amendments) and in accordance with clinical sites Standard Operating Procedures, International Council for Harmonization Good Clinical Practice, all other applicable regulations, and the recommendations laid down in the most recent version of the Declaration of Helsinki.

Signature of Principal Investigator	Date
Printed Name of Principal Investigator	

SUMMARY OF REVISIONS

Document	Version and Date	Key Changes	Rationale
Amendment version	3.0 02Feb2024	Page 7, update the estimated total number of randomized patients.	To ensure approximately 60 patients completing treatment during the study.
		Page 74, Section 5.8. add the following language for clarification: ...only data from acceptable spirometry maneuvers will be used for eligibility confirmation and data analysis. For baseline and EOT visits, if multiple acceptable spirometry results are reported for one visit, mean values of the acceptable results will be used for data analysis. For detailed information, refer to the statistical analysis plan	Clarification of spirometry data management method.
		Page 77-78, Section 5.12, add the following language: In addition, high-throughput proteomic analysis will be performed to further explore the mechanism of action of INS018_055 in IPF patients.	Add high-throughput proteomic analysis as a method for exploratory endpoints.
		Page 103, Section 10.3, update the format of Borg Scale CR10 form	Update the Borg Scale CR10 form to be consistent with the purchased copyrighted version.

CLINICAL TRIAL PROTOCOL

Protocol Number	INS018-055-003	
InSilico Investigational Medicinal Product	INS018_055 capsule	
Title	A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of INS018_055 Administered Orally to Subjects with Idiopathic Pulmonary Fibrosis (IPF)	
Lay Title	A study to test INS018_055 safety and how taking INS018_055 over 12 weeks affects the lung function of adults with idiopathic pulmonary fibrosis	
Sponsor	InSilico Medicine Hong Kong Limited Unit 310, F3, Building 8W, Phase 2, Hong Kong Science Park, Pak Shek Kok, New Territories, Hong Kong	
Study Phase	IIa	
Study Sites	About 30 sites in China	
Indication	Idiopathic pulmonary fibrosis	
Version and Date	**4.0**	**Date: 02Feb2024**

PROTOCOL SYNOPSIS

Company Name	InSilico Medicine Hong Kong Limited
Protocol version 1.0 Date	04Nov2022
Version 2.0 Date	28Dec2022
Version 2.2 Date	08May2023
Version 3.0 Date	18Aug2023
Version 4.0 Date	02Feb2024
Protocol Number	INS018-055-003
Study Title	A Phase IIa, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics, and Efficacy of INS018_055 Administered Orally to Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Study Site(s)	Multicenter trial at an estimated 30 sites in China
Clinical Phase	IIa
Study Rationale	The purpose of this study is to demonstrate safety and proof of concept for clinical activity of INS018-055 on change in forced vital capacity (FVC) over 12 weeks in adults with idiopathic pulmonary fibrosis (IPF). IPF is a fatal lung disease characterized by reduced quality of life and a median survival of 3 to 4 years. While current standard of care (SoC) treatments including pirfenidone and nintedanib slow disease progression, they are not curative and poorly tolerated due to their toxicity profiles. To address the need for new treatments in IPF, InSilico Medicine is developing INS018_055, a potent inhibitor of the serine/threonine kinase Traf2- and Nck-interacting kinase (TNIK). INS018_055 modulates the Wnt signaling pathway and engages other IPF-related signaling pathways. Wnt signaling is consistently identified as a major signaling cascade that significantly contributes to the pathogenesis of lung fibrosis. Therefore, TNIK is a clinically meaningful therapeutic target and INS018_055 could potentially address the unmet need in IPF for novel treatments.
Study Objectives	Primary Objective: ● To evaluate the safety and tolerability of INS018_055 orally administered for up to 12 weeks in adult patients with IPF compared to placebo Secondary Objectives:

	• To evaluate the pharmacokinetics (PK) of INS018_055 orally administered to subjects with IPF • To evaluate the efficacy of INS018_055 orally administered for up to 12 weeks of treatment on FVC decline in adult subjects with IPF compared to placebo • To evaluate the efficacy of INS018_055 orally administered for up to 12 weeks of treatment to improve quality of life (QoL) and functional measures compared to placebo • To evaluate the impact of INS018_055 orally administered on acute IPF exacerbations compared to placebo Exploratory Objective: • To explore the impact of INS018_055 on IPF disease-related biomarkers in the blood • To explore the potential mechanism of action of INS018_055 in IPF patients
Study Endpoints	The primary endpoint is the percentage of patients who have at least 1 treatment-emergent adverse event (TEAE). The secondary endpoints are PK parameters, change in FVC (mL and % predicted), change in diffuse capacity of the lungs for carbon monoxide (DLCO %) predicted, change in Leicester Cough Questionnaire, change in 6-minute walk test (6MWD), number of acute IPF exacerbations, and number of hospitalization days for acute exacerbations.
Study Design	Randomized, double-blind, placebo-controlled, parallel-group design of 4 groups over 12 weeks
Total Number of Patients Randomized	Approximately 70 (approximately 60 to complete treatment)
Number of Patients on Each Treatment	Approximately 15
Diagnosis	Idiopathic pulmonary fibrosis
Key Study Criteria	All inclusion criteria and no exclusion must be met for study enrollment. See detailed list in section 3.3.2 (inclusion criteria) and section 3.3.3 (exclusion criteria). Key inclusion criteria: ● Patients aged $\geq$ 40 years at screening ● Diagnosis of IPF confirmed by site investigator ● FVC $\geq$ 40% predicted normal at Visit 1 ● DLCO $\geq$ 25% and < 80% at Visit 1

	• Pre-bronchodilator FEV1/FVC ratio > 0.7 (absence of relevant airway obstruction) • Ability to walk ≥ 150 meters for 6MWD at Visit 1 • Either stable treatment with background SoC pirfenidone or nintedanib for ≥ 8 weeks prior to Visit 1 or prior treatment with SoC pirfenidone or nintedanib discontinued for ≥ 4 weeks prior to Visit 1 • Subjects who have previously never received SoC treatment with pirfenidone or nintedanib are eligible to participate provided they meet all other eligibility criteria and have discussed all SoC treatment options with their physician • Compliance with study protocol Key exclusion criteria: • Investigator-determined clinically significant airway disease that could impact study objectives • Acute IPF exacerbation < 4 months prior to Visit 1 and/or during the screening period • Upper or lower respiratory tract infection that has not fully resolved within 4 weeks prior to Visit 1 and/or before Visit 2 (Day 1). (section 3.3.3) • COVID-19: RT-PCR-confirmed or rapid antigen test confirmed infection at Visit 1or at Visit 2; vaccine within the last 7 days of Visit 2; severe infection requiring hospitalization within the last 6 months of screening; symptoms > 12 weeks of acute infection (Long COVID-19) • Current smoker or prior smoker with nicotine or tobacco use ≤ 3 months prior to Visit 1 • Unstable cardiac angina or myocardial infarction < 6 months prior to Visit 1 • Documented active or suspected malignancy or history of malignancy < 5 years prior to Visit 1, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of the uterine cervix, or prostate cancer under surveillance • Significant trauma or major surgery < 3 months prior to Visit 1 • Medications: -Concurrent treatment with nintedanib and pirfenidone is not allowed during the study unless the patients have had a stable treatment with one of them for ≥8 weeks prior to visit 2 -Current oral corticosteroids > 15 mg prednisone daily (or equivalent) or combination of prednisone, azathioprine, and

	N-acetylcysteine, ambrisentan, or imatinib ≤ 30 days prior to Visit 2 -Current moderate or strong CYP3A4 inhibitors/inducers, moderate or strong CYP1A2 inhibitors/inducers, or medications primarily metabolized by CYP3A4 or CYP1A2 -Current enrollment or prior participation in interventional clinical studies < 30 days or 5 half-lives of investigational therapy (whichever is longer) prior to Visit 1 ● Investigator-determined medical or psychological condition that might create undue risk or interfere with study compliance, including but not limited to pulmonary hypertension, active lung transplantation registration, uncontrolled hypertension, laboratory values (e.g. BMI, AST/ALT, total bilirubin, eGFR, QTc), known hypersensitivity or contraindications to INS018_055 or its class, pregnant or lactating, substance abuse, chronic liver disease, HIV+ history, active HCV, active HBV, or other active infection
Investigational product(s)	INS018_055 capsule
Dose(s)	30 mg QD or 30 mg BID or 60 mg QD (maximum 60 mg daily): ● 30 mg QD INS018_055 ● 30 mg BID INS018_055 ● 60 mg QD INS018_055
Administration	Oral
Comparator product(s)	Placebo
Dose(s)	Matching placebo
Administration	Oral
Duration of Treatment	12 weeks
Statistical Methods	Safety Population: The safety population will include all subjects who receive ≥ 1 dose of study treatment. ITT Population: The intent-to-treat (ITT) population will include any randomized subjects. PK Population: The PK population will include subjects who receive ≥ 1 dose of study treatment and have a majority of

	scheduled PK samples drawn that allow for PK parameters to be generated. Per Protocol (PP) Population: The PP population will exclude non-evaluable subjects and subjects with major protocol deviations thought to impact the ability to assess the effect of study treatment. The criteria for excluding subjects from the PP population will be specified in the Statistical Analysis Plan (SAP). A formal sample size calculation based on statistical power considerations will not be performed. However, given an approximate sample size of 15 subjects per treatment arm, there exists a 90% probability of observing ≥ 1 AE if the true population rate is approximately 15%, which will be sufficient to assess the feasibility of safety parameters. Demographic and Baseline Characteristics: The ITT population will be used for summary of demographic and baseline characteristics. Demographic characteristics (e.g., age, sex, ethnicity, race, etc.) and screening clinical characteristics (e.g., vital signs, physical examination, etc.) will be summarized using descriptive statistics [number of patients (n), mean, standard deviation (SD), median, minimum (min), and maximum (max)] for continuous variables, and using counts (%) for categorical variables. Baseline laboratory results will be summarized overall and by treatment arm using descriptive statistics. Additionally, the proportion of subjects on antifibrotic or not on antifibrotic therapy at the time of randomization for each treatment arm will be summarized. Safety Endpoints: All safety analyses will be performed on the safety population. The analysis of safety endpoints, including AEs, SAEs, TEAEs and AEs of interest (coded using the Medical Dictionary for Regulatory Activities [MedDRA®]), will be summarized by System Organ Class, Preferred Terms, and their maximum severity based on CTCAE v5.0 grade for all treated subjects. Clinical laboratory tests, physical examination, ECGs, and vital signs will be summarized or tabulated by treatment arm and visit, and will also be presented in shift tables.

SCHEDULE OF STUDY ACTIVITIES

The table below shows the overall order of procedures by visit. See section 5.1 for details about order of procedures within each visit.

Trial Period	**Screening[a]**	**Treatment Period[b]**					**Follow-up**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6 (EOT)**	**7 (EOS)**
Study Week		**0**	**2**	**4**	**8**	**12**	**13**
Study Day	**-30 to 0**	**1**	**15**	**29**	**57**	**85**	**92**
Visit Window (days)[c]	**-**	**-**	**± 3**	**± 7**	**± 7**	**± 7**	**+10**
Informed consent[d]	X						
Demographics	X						
Medical history	X						
HRCT[e]	X						
HBV, HCV, HIV, syphilis testing[f]	X						
Height	X						
Spirometry (FEV1, FVC)[g]	X	X				X	
DLCO[h]	X	X				X	
6MWD	X	X				X	
SARS-CoV-2 testing[i]	X	X					
Assess eligibility criteria	X	X					
BMI	X	X				X	
12-lead ECG[j]	X	X	X	X	X	X	
Physical examination[k]	X	X	X	X	X	X	X
Vital signs[l]	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Pregnancy testing[m]	X	X	X	X	X	X	X
Safety laboratory tests[n,o]	X	X	X	X	X	X	X
Urinalysis[p]	X	X	X	X	X	X	X
Adverse events[q]	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X
Randomization		X					
LCQ[r]		X		X	X	X	
Pharmacokinetic (PK) sampling[s]		X	X	X	X	X	

Trial Period	**Screening[a]**	**Treatment Period[b]**					**Follow-up**
Visit Number	**1**	**2**	**3**	**4**	**5**	**6 (EOT)**	**7 (EOS)**
Study Week		**0**	**2**	**4**	**8**	**12**	**13**
Study Day	**-30 to 0**	**1**	**15**	**29**	**57**	**85**	**92**
Visit Window (days)[c]	**-**	**-**	**± 3**	**± 7**	**± 7**	**± 7**	**+10**
Dispense study drug		X	X	X	X		
Self-administer study drug[t]		----------X----------					
Subject study diary[u]		----------X----------					
IPF biomarker (PD) sampling (blood, pre-dose)[v]		X	X	X	X	X	
PK of SoC therapy[w]		X	X	X	X	X	
Acute IPF exacerbations[x]		X	X	X	X	X	X
Drug accountability and compliance[y]			X	X	X	X	
Completion of patient participation							X

[a] Screening (Visit 1) should be conducted up to 30 days prior to Visit 2 (randomization), with time allowed for central review of HRCT (performed during the screening period or within the last 12 months) or surgical lung biopsy to confirm eligibility (if HRCT is equivocal). This period may be extended up to 44 days in case of administrative issue (e.g. result from HRCT is not available). If Visit 1 cannot be performed in this extended timeframe, the patient will have to be considered a screen fail.

[b] Subjects who discontinue study medication will be asked to attend all study visits as originally planned in order to minimize missing data. If subject declines, all activities scheduled for the EOT visit (Visit 6) should be performed if possible. The last morning dose in the study is considered the last study dose. All subjects will be asked to return all unused medication at Visit 6/EOT.

[c] All efforts should be made to maintain protocol-defined visit windows. If an extenuating circumstance arises preventing this, the Sponsor and/or designee should be consulted. If the Sponsor and/or designee determines that the scientific integrity of data and patient safety would not be compromised, an out-of-window visit may be permitted.

[d] Informed consent must be obtained before study-related procedures are performed, including HRCT review. All AEs will be recorded from the signing of the ICF. All non-serious ongoing AEs that occurred prior to the time of first dose will be captured as medical history.

[e] Central review of HRCT will be performed. A historical HRCT performed within 12 months of screening (Visit 1) should be evaluated for eligibility. If an HRCT performed within the last 12 months is not available or does not meet required image acquisition specifications and the patient meets all other eligibility criteria, HRCT should be performed during the screening period.

[f] Including HBsAg, anti-HCV, hepatitis B viral load DNA, and hepatitis C viral load RNA (if applicable), anti-HIV-1, anti-HIV-2, and syphilis. Patients who are known to be hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (HBcAb) positive will undergo hepatitis B viral load DNA by PCR. Patients who are known to be hepatitis C virus (HCV) antibody positive must undergo hepatitis C viral load RNA by PCR.

[g] Spirometry results to be reviewed centrally to meet American Thoracic Society-European Respiratory Society criteria 2019 guideline. Order of lung function measurements: 1. Spirometry followed by patient rest; 2. DLCO.

[h] DLCO % predicted to be corrected for hemoglobin level and conducted with equipment at each study site, carried out according to international guidelines.

[i] SARS-CoV-2 testing to be performed at screening (Visit 1) and prior to randomization at Visit 2. Both SARS-CoV-2 RT-PCR testing and rapid antigen test are acceptable.

[j] All ECGs will be performed pre-dose.

[k] A complete physical examination will be completed at screening and symptom-specific physical examinations will be completed for other visits.

[l] Measurements of vital signs should precede blood sampling.

[m] Female with childbearing potential only: urine pregnancy test at each visit, except at Screening (Visit 1). Serum pregnancy test will be performed at screening visit.

[n] For laboratory parameters that initially do not meet eligibility requirements, a single retest within the screening period is permitted before subject is declared a screen failure.

[o] Safety laboratory parameters will be evaluated at each visit, pre-dose. This will include blood and urine. Serum chemistry analysis includes AST, ALT, AP, GGT, CK (CK-MB only if CK is elevated), glucose, creatinine, total bilirubin, direct and indirect bilirubin, total protein, albumin, hsCRP, BUN or urea, uric acid. Electrolyte analysis includes sodium, potassium, calcium, chloride, inorganic phosphate. Hematology includes hematocrit, hemoglobin, RBC count, reticulocyte count, WBC with differential (automatic WBC differential includes the relative and absolute quantification of neutrophils, eosinophils, basophils, monocytes and lymphocytes). If automatic WBC differential is abnormal, manual WBC differential is advised to include polymorphonuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes and lymphocytes, platelet count, ESR. Lipid panel to include total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol,. Coagulation panel includes aPTT, Prothrombin time (Quick's test and INR), and fibrinogen. Hormone tests include thyroid stimulating hormone (TSH), fT3, fT4. eGFR by CKD-EPI equation.

[p] Urinalysis to include qualitative/semi-quantitative, appearance, color, pH, specific gravity, glucose, erythrocytes, leukocytes, protein, urobilinogen, urine bilirubin.

[q] Acute IPF exacerbation will be defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality with all of the following: Acute worsening or development of dyspnea typically for < 1 month duration, CT scan with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with IPF, deterioration not fully explained by cardiac failure or fluid overload. [Collard 2016] Events that are clinically considered to meet the definition of acute exacerbation but fail to meet diagnostic criteria due to missing CT data should be termed "suspected acute exacerbations".

[r] The Leicester Cough Questionnaire (LCQ) is a 19-item questionnaire that assesses cough related QoL. It has 3 domains (physical, psychological, and social). The total score range is 3-21, and domain scores range from 1-7; a higher score indicates a better QoL. The overall score for the LCQ for each subject is calculated by adding the individual domain scores. The LCQ will be self-administered by subjects at the indicated visits.

[s] Blood samples for plasma concentrations of INS018_055 and metabolites (INS018_063 and INS018_095) will be collected at time points according shown in section 10.4. Date and exact clock time of drug administration and blood sampling must be recorded on the eCRF.

[t] Subjects will self-administer study medication. Site team will explain dosing schedule, provide study medication, and follow up with subjects.

[u] Subjects will maintain a study diary throughout study. Site team will instruct subject to record precisely the time of drug intake.

[v] Including evaluation of levels of MMP-7, MMP-2, MMP-9, TGF-beta, IL-6, TIMP-1, IL-1beta in blood samples and evaluation of blood proteome.

[w] Blood samples for plasma concentrations of SoC therapy will be collected pre-dose (ie, prior to pirfenidone or nintedanib dosing), in order to get the trough plasma concentration of SoC therapy at Visit 2, 3, 4, 5, and 6.

[x] Investigator-reported acute IPF exacerbations to be reported in the eCRF.

[y] Collect unused previously dispensed study drug at each visit

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ABBREVIATIONS

%CV	Percent Coefficient of Variation
aPTT	Activated Partial Thromboplastin Time
ADL	Activities of Daily Living
ADME	Absorption, Distribution, Metabolism, and Elimination
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AP	Alkaline phosphatase
AST	Aspartate Aminotransferase
ATS	American Thoracic Society
AUC	Area Under the Curve
BALF	Broncho-Alveolar Lavage Fluid
BID	bis in die (twice daily dosing)
BLM	Bleomycin
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CA	Competent Authority
CI	Confidence interval
CK	Creatine kinase
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CYP	Cytochrome P450
DDI	Drug Drug Interaction
DDR1	Discoidin Domain Receptor 1
DLCO	Diffusion Capacity of the Lung for Carbon Monoxide
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
ESR	Erythrocyte Sedimentation Rate
eCRF	electronic Case Report Form

EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EOS	End of Study
EOT	End of Treatment
FDA	Federal Drug Administration
FEV1	Forced Expiratory Volume in one second
FOBT	Fecal Occult Blood Testing
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCV	Geometric Coefficients of Variation
GGT	Gamma-glutamyl transferase
GI	Gastro Intestinal
GMP	Good Manufacturing Practice
HA	Health Authority
HR	Heart Rate
HRCT	High Resolution Computed Tomography Scan
HBcAb	Hepatitis B core Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B
HCV	Hepatitis C
HDL	High-Density Lipoprotein
HIV	Human Immunodeficiency Virus
hsCRP	high sensitivity C-Reactive Protein
HV	Healthy Volunteers
IC50	Half maximal Inhibitory Concentration
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IL	Interleukin
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITT	Intention to treat
LCQ	Leicester Cough Questionnaire
LDH	Lactate dehydrogenase
LDL	Low-Density Lipoprotein
LFT	Liver Function Test
LMM	Linear Mixed Effect Model
LPLT	**Last Patient Last Treatment**
LPS	lipopolysaccharides
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model Repeated Measures
MNAR	Missing Not At Random
NOAEL	No Observed Adverse Effect Level

NZ	New Zealand
PBPK	Physiologically-based Pharmacokinetic
PFT	Pulmonary Function Test
PCR	Polymerase Chain Reaction
PFT	Pulmonary Function Test
PK	Pharmacokinetics
PoC	Proof of Concept
PP	Per Protocol
PRO	Patient Reported Outcome
PV	Pharmacovigilance
PY	Person-Year
QD	every day
QoL	Quality of Life
RA	Regulatory Authority
RBC	Red Blood Cell
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
T_{max}	Time to reach Maximum Plasma Concentration
TEAE	Treatment Emergent Adverse Event
TGF	Transforming Growth Factor
TSH	Thyroid Stimulating Hormone
ULN	Upper Level of Normal
UIP	Usual Interstitial Pneumonia
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman Of Childbearing Potential
6MWD	6-Minute Walk Distance

1 INTRODUCTION

INS018_055 is a potent inhibitor of the serine/threonine kinase Traf2- and Nck-interacting kinase (TNIK) that can manipulate the aberrant Wnt signaling pathway and engage other IPF-related signaling pathways, including NF-κB and TGF-β. It is under development for the treatment of idiopathic pulmonary fibrosis (IPF).

1.1 MEDICAL BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a fatal lung disease, characterized by distorted lung architecture and loss of respiratory function as a result of alveolar epithelial cell injury and hyperplasia, enhanced extracellular matrix deposition, and myofibroblast activation. IPF carries a poor prognosis with a median survival of 3 to 4 years. [Fernández Pérez 2010] [Strongman 2018].

IPF occurs worldwide. The prevalence of IPF appears to be increasing, although it is unclear whether this reflects increased recognition or a true increase in incidence. The incidence of IPF appears to be higher in North America and Europe [3 to 9 cases per 100,000 person-years (PY)] than in South America and East Asia (fewer than 4 cases per 100,000 PYs). [Hutchinson 2015] In the U.S., the prevalence of IPF has been reported to range from 10 to 60 cases per 100,000. [Esposito 2015] [Raghu 2016] [Raghu 2014] Increasing rates of hospital admissions and deaths due to IPF also suggest an increasing burden of disease. [Hutchinson 2015] [Hutchinson 2014] [Lee 2014]

Pirfenidone and nintedanib are antifibrotic therapies approved for the treatment of IPF and can slow disease progression. [Richeldi 2014] [Flaherty 2019] However, currently available therapies are not curative and are associated with side effects, including gastrointestinal (GI) side effects, liver injury, photosensitivity rash, change in taste and smell perception (pirfenidone only), bleeding risk (nintedanib only). [Richeldi 2014] [Flaherty 2019] [Proesmans 2019] [Grześk 2020] Real world data suggests that 20 to 27% of patients discontinue treatment with approved therapy due to adverse effects or poor tolerability. [Galli 2017] [Strens 2021] New treatments that further slow disease progression and expand treatment options for patients unable to tolerate currently approved treatments are needed. [Chambers 2022] [Somogyi 2019]

1.2 DRUG PROFILE

1.2.1 Mode of Action

INS018_055 is a potent inhibitor of the serine/threonine kinase Traf2- and Nck-interacting kinase (TNIK) that can reduce idiopathic pulmonary fibrosis in adults. The serine/threonine

kinase TNIK, first identified as a regulatory kinase in cell spreading or migration through cytoskeleton organization, is a member of germinal center kinases (GCKs) possessing the N-terminal kinase domain, an intermediate domain, and a C-terminal germinal center kinase homology (GCKH) region and interacts with important signal transduction cascades where its mechanisms of action include:

- Modulation of Wnt-induced gene expression program together with Transcription Factor 7 Like 2 (TCF7L2)
- Co-operation within c-Jun N-terminal kinase (JNK) and mitogen-activated protein kinase (MAPK) pathway
- Other interactions and cross-talks with nuclear factor kappa B (NF-κB) and TGF-β pathways

Of all the signaling pathways where TNIK acts, Wnt signaling is consistently identified as a major activated signaling cascade that significantly contributes to the pathogenesis of lung fibrosis. [Morrisey 2003] [Baarsma 2018] Therefore, TNIK is a feasible target of pharmacologic intervention in IPF.

1.2.2 Key Pharmacokinetic Characteristics

Two phase 1, randomized, double-blind, placebo-controlled, parallel-group, single ascending dose (SAD) and multiple ascending dose (MAD) studies were conducted to evaluate the safety, tolerability, pharmacokinetic (PK), food effects, and drug-drug interaction (DDI) potential of INS018_055 in healthy subjects in New Zealand (NZ) (NCT05154240) and China (CTR20221542).

PK summary for phase 1 study in New Zealand (NCT05154240)
The PK data of INS018_055 for all SAD and MAD cohorts showed a dose-proportional increase of the plasma exposure over the single-dose range of 10 to 120 mg and no significant accumulation after 7-day every day (QD) oral administrations when the steady state was reached. Food effect on the PK of INS018_055 was assessed at the single dose of 90 mg. Compared to fasted conditions, food decreased C_{max} and AUC_{0-t} by approximately 38% and 14%, respectively, and prolonged T_{max} from 1 to 3 hours. The PK parameters of INS018_055 for SAD cohorts in the NZ study are shown Table 1. Three MAD cohorts were also completed and the PK parameters are shown in below Table 2.

Table 1. Plasma PK Parameters of INS018_055 in SAD Cohorts in Study in New Zealand

PK Parameter	INS018_055 10 mg (N=6)	INS018_055 30 mg (N=6)	INS018_055 60 mg (N=6)	INS018_055 90 mg Fasted (N=6)	INS018_055 90 mg Fed (N=6)	INS018_055 120 mg (N=6)
C_{max} (ng/mL)	25.4 (66.8)	105 (44.4)	273 (47.5)	270 (44.1)	169 (42.8)	339 (32.1)
T_{max} (h)	1.0 (1.0-2.0)	1.53 (1.0-4.0)	1.0 (0.5-2.0)	1.01 (0.5-2.0)	3.0 (2.0-4.0)	1.5 (1.0-2.0)
AUC_{0-t} (ng*h/mL)	124 (69.3)	552 (46.0)	1210 (61.0)	1620 (40.5)	1390 (44.9)	1980 (35.1)
$T_{1/2}$ (h)	9.72 (23.8)	7.42 (9.30)	7.96 (23.6)	8.61 (48.9)	9.71 (35.0)	9.74 (39.2)
CL/F (L/h)	74.2 (63.3)	53.7 (45.7)	49.1 (61.0)	55.2 (40.4)	64.1 (44.6)	60.0 (35.1)
Vd/F (L)	1040 (68.7)	575 (39.2)	563 (39.9)	685 (29.2)	898 (22.9)	843 (61.0)

Table 2. Plasma PK Parameters of INS018_055 in MAD Cohorts in Study in New Zealand

PK Parameter[a]	INS018_055 30 mg QD (N=6 for Day 1, N=5 for Day 7)		INS018_055 60 mg QD (N=6)		INS018_055 120 mg QD (N=6)	
Day	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
C_{max} (ng/mL)	106 (28.1)	79.4 (50.1)	226 (24.1)	191 (36.5)	511 (13.5)	463 (26.5)
T_{max} (h)	1.0 (1.0-1.0)	1.0 (1.0-1.98)	1.0 (1.0-2.0)	1.5 (0.52-2.0)	1.5 (1.0-4.0)	2.0 (1.0-2.0)
$AUC_{0-\tau}$ (ng*h/mL)	404 (34.8)	439 (39.8)	1150 (25.3)	1210 (29.9)	3050 (24.9)	3040 (25.3)
$T_{1/2}$ (h)	5.80 (8.32)	9.36 (24.4)	-	11.9 (13.9)	-	10.2 (11.4)
ARC_{max}[b]	-	0.739 (25.9)	-	0.843 (33.0)	-	0.905 (21.7)
ARAUC[c]	-	1.02 (20.0)	-	1.05 (5.81)	-	0.996 (3.66)

[a] Values are presented as the geometric mean (geometric CV%), except for T_{max} shown as the median (min-max).
[b] ARC_{max} derived as C_{max} Day 7 / C_{max} Day 1.
[c] ARAUC derived as $AUC_{0-\tau}$ Day 7 / $AUC_{0-\tau}$ Day 1.

PK summary for phase 1 study in China (CTR20221542)

The other phase I, randomized, double-blind, placebo-controlled, parallel-group, SAD and MAD study to evaluate the safety, tolerability, and pharmacokinetics of INS018_055 in healthy subjects in China (CTR20221542) has also been completed. In the SAD part, 24 subjects were given a single dose of INS018-055 30 mg, 60 mg, 120 mg or placebo control (8 subjects/cohort with a INS018-055 treatment to placebo ratio of 3 to 1). In the MAD part, 32 subjects were given multiple doses of INS018-055 30 mg twice daily (BID), 60 mg BID, 90 mg BID or placebo control for 7 days (8 subjects/cohort with a treatment to placebo ratio

of 3 to 1). The study objectives (primary, secondary, exploratory) and analysis plan are similar to the SAD part and the MAD part of the NZ study (NCT05154240).
After healthy subjects received INS018_055 capsule administration, PK exposure of INS018_055, INS018_063, and INS018_095 in the SAD and MAD phases increased with dose but did not show a complete dose-linear relationship. After 7 consecutive days of BID oral administration of INS018_055 capsules, INS018_055 and INS018_095 were essentially stabilized, whereas the trough concentrations of INS018_063 tended to increase at D2-D7. No significant accumulation was observed for INS018_055 and INS018_095, except for INS018_063, which had an accumulation ratio of >1 and <5 for systemic exposure. In addition, the PK profile of INS018-055 in this study was similar to those in the New Zealand study with no significant differences.

1.2.3 Drug Drug Interactions

The CYP3A4 pathway will significantly affect INS018_055, which is primarily metabolized by CYP3A4 based on *in vitro* data. The DDI potential of INS018_055 to induce CYP1A2 expression is currently being studied (NCT05154240).

Given the potential CYP3A4- and CYP1A2-mediated DDIs with permitted SoC antifibrotic treatments (pirfenidone, nintedanib), including with INS018_055, concurrent moderate/strong CYP3A4 inhibitors/inducers or medications primarily metabolized by CYP3A4 are not permitted. Moderate/strong CYP1A2 inhibitors/inducers or medications primarily metabolized by CYP1A2 are also not permitted.

Pirfenidone *in vitro* profiling studies in hepatocytes and liver microsomes indicate it is primarily metabolized in the liver by CYP1A2 with minor contributions from other CYP isozymes (CYP2C9, 2C19, 2D6, and 2E1). Concomitant use of pirfenidone and a moderate/strong CYP1A2 inhibitor/inducer could change the exposure of pirfenidone.

Nintedanib is mainly metabolized by esterases. *In vitro*, CYP-dependent metabolism accounted for about 5% (CYP 3A4 predominant enzyme) compared to about 25% ester cleavage. The major CYP-dependent metabolite could not be detected in plasma in the human ADME study. Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Concomitant use of nintedanib and a CPY3A4 inhibitor/inducer may change the exposure of nintedanib.

1.2.4 Data From Non-Clinical Studies

The biological activities of INS018_055, a potent inhibitor of the serine/threonine kinase TNIK, has been fully characterized. INS018_055 showed potent inhibition of TNIK in a biochemical enzymatic assay with an IC_{50} value of 23 nmol/L. INS018_055 inhibited a few

other kinases that are known to be involved in pro-fibrotic pathways, i.e., ALK4, DDR1, FMS, TGFBR1. INS018_055 potently inhibited TGF-β-induced expression of α-SMA, fibronectin and PAI-1 in MRC-5 cells (a lung fibroblast cell line). INS018_055 showed concentration-dependent inhibition of TGF-β1-mediated α-SMA expression in primary lung fibroblasts (FMT assay) and fibronectin expression in primary bronchial epithelial cells (EMT assay) derived from IPF patients.

INS018_055 (3 mg/kg BID, 10 mg/kg BID, 30 mg/kg BID) exerted anti-inflammatory and anti-fibrotic effects in bleomycin (BLM)-induced lung fibrosis mouse model and significantly improved the lung function impaired by BLM. In a combination therapy study using a BLM-induced lung fibrosis mouse model, INS018_055 3 mg/kg BID exerted additive effect when combined with the suboptimal dose of pirfenidone 60 mg/kg BID. [redacted] In a second combination therapy study, the group treated with INS018_055 10 mg/kg BID and optimal dose of pirfenidone 200 mg/kg BID showed the best improvement in body weight loss recovery and lung function. [redacted] In a study conducted in a lipopolysaccharides (LPS)-induced acute lung injury mouse model, INS018_055 suppressed proinflammatory cytokines, which were elevated post-LPS challenge; INS018_055 increased anti-inflammatory cytokine levels, which were decreased post-LPS challenge. The antifibrotic effect of INS018_055 was also validated in a widely used kidney fibrosis model, i.e., mouse unilateral ureteral obstruction model, which has the pathological features of chronic kidney disease including interstitial fibrosis.

Overall, INS018_055 pre-clinical studies showed potent anti-fibrotic and anti-inflammatory activities in lung and rescued loss of lung function.

1.2.5 Data From Clinical Studies

Two phase 1 trials in New Zealand (NCT05154240) and China (CTR20221542) have been completed and the clinical study reports are available.

Safety summary for phase 1 study in New Zealand (NCT05154240)

For the phase 1 study in New Zealand, 78 healthy volunteer subjects were dosed with INS018_055 or placebo. This included 40 subjects in SAD cohorts (Part A) who received the single dose of 10 mg, 30 mg, 60 mg, 90 mg, or 120 mg (8 subjects in each cohort: 2 from the sentinel group and 6 from the rest of cohort group), and 24 subjects in MAD cohorts (Part B)

who received the multiple doses of 30 mg QD, 60 mg QD or 120 mg QD, respectively for up to 7 days (8 subjects in each cohort). For DDI (Part C) study, 14 healthy participants received a single oral dose of caffeine 200 mg on Day one, followed by a washout from Day two to four, and subsequently received multiple oral doses of INS018_055 120 mg QD for 14 days (Day five through 18) with a single oral dose of caffeine 200 mg on Day 18.

SAD Part (Part A)
Administration of a single dose of INS018_055 (10 mg, 30 mg, 60 mg, 90 mg, or 120 mg) under fasted conditions and a single dose of INS018_055 (90 mg) under fed conditions was safe and generally well tolerated by the healthy subjects in this study.

There were no deaths or SAEs during the study, and no subject discontinued the study treatment due to TEAEs. No dose-related trends were observed.

Overall, 11 of 30 subjects (36.7%) who received INS018_055 and 4 of 10 subjects (40.0%) who received placebo experienced at least 1 TEAE. A total of 21 TEAEs (14 TEAEs in subjects who received INS018_055 and 7 TEAEs in subjects who received placebo) were reported. All TEAEs were of mild severity and resolved.

Most reported TEAEs in subjects who received INS018_055 were phlebitis reported in 3 subjects (10.0%), fecal occult blood positive and medical device site irritation reported in 2 subjects (6.7%) each, and all remaining TEAEs were reported in 1 subject (3.3%) each.

Four subjects (13.3%) who received INS018_055 and 4 subjects (40.0%) who received placebo experienced TEAEs that were considered related to the study treatment.

No clinically significant results were observed for clinical laboratory evaluations; however, positive test results were noted for fecal occult blood and reported as mild TEAEs.

No treatment-related trends were observed in 12-lead ECG measurements. No abnormal ECG finding was clinically significant. None of the individual hematology, serum chemistry, urinalysis values, vital signs, or 12-lead ECG measurements were considered clinically significant or were reported as a TEAE by the investigator.

MAD part (Part B)

Administration of INS018_055 QD for 7 days under fasted conditions (30 mg, 60 mg, or 120 mg) was safe and generally well tolerated by the healthy subjects in this study.

There were no deaths or SAEs during the study. One subject discontinued the study treatment due to a moderate TEAE of influenza-like illness. No dose-related trends were observed in TEAEs.

Overall, 16 of 18 subjects (88.9%) who received INS018_055 and 5 of 6 subjects (83.3%) who received placebo experienced at least 1 TEAE. A total of 55 TEAEs (46 TEAEs in subjects who received INS018_055 and 9 TEAEs in subjects who received placebo) were reported. Most reported TEAEs in subjects who received INS018_055 were headache reported in 10 subjects (55.6%), fecal occult blood positive in 7 subjects (38.9%), upper respiratory tract infection in 3 subjects (16.7%), and all remaining TEAEs were reported in 1 subject (5.6%) each.

One subject was reported with a moderate TEAE; all other TEAEs were mild. All TEAEs resolved, except for a mild TEAE of seasonal allergy reported in INS018_055 60 mg cohort that did not resolve and a mild TEAE of COVID-19 in INS018_055 30 mg cohort which was resolving by end of the study. The TEAEs of seasonal allergy and COVID-19 were not related to the study treatment.

Thirteen subjects (72.2%) who received INS018_055 and 1 subject (16.7%) who received placebo experienced TEAEs that were considered related to the study treatment.

Changes observed in serum chemistry were mild. Positive test results were noted for fecal occult blood and reported as mild TEAEs. All changes were transient and resolved within the study duration.

No treatment-related trends were observed in 12-lead ECG measurements. None of the individual hematology, urinalysis values, vital signs, or 12-lead ECG measurements were considered clinically significant or were reported as a TEAE by the investigator.

DDI part (Part C)

Administration of a single dose of caffeine (200 mg) with INS018_055 (120 mg) was generally safe and well tolerated by the healthy subjects in this study.

There were no deaths, SAEs or TEAEs leading to early discontinuation in Part C of the study with the exception of 1 subject who discontinued treatment due to a moderate TEAE of ALT increase.

Overall, 8 of 14 subjects (57.1%) in Period 1 (caffeine) and 14 of 14 subjects (100.0%) in Period 2 (caffeine+INS018_055 120mg) experienced at least 1 TEAE, in which 2 subjects (14.3%) in Period 1 (caffeine) and 14 subjects (100.0%) in Period 2 (caffeine+INS018_055 120mg) experienced TEAEs that were considered related to the study treatment. In total 99

TEAEs (9 TEAEs in subjects in Period 1 [caffeine] and 90 TEAEs in subjects in Period 2 [caffeine+INS018_055 120mg]) were reported, in which 2 TEAEs in Period 1 (caffeine) and 61 TEAEs in Period 2 (caffeine+INS018_055 120mg) were considered related to the study treatment. Most reported TEAEs in subjects during Period 1 (caffeine) were headache and catheter site phlebitis in 3 subjects (21.4%) each; In Period 2 (caffeine+INS018_055 120mg), the most reported TEAEs were headache in 13 subjects (92.9%). TEAEs were reported in 3 subjects (21.4%) for the following: nausea, fatigue, increased ALT, increased AST and fecal occult blood positive. All other TEAEs were reported in ⩽ 2 subjects.

All TEAEs were mild in severity with the exception of one subject with moderate elevation of ALT in Period 2 (caffeine+INS018_055 120 mg) that retuned to baseline. All other TEAEs resolved, except for mild TEAEs of mouth ulceration and rash (non-erythematous) reported in one subject and a mild TEAE of erythematous rash reported in another subject in Period 2 (caffeine+INS018_055 120 mg). The TEAEs of mouth ulceration and rash erythematous were related to the study treatment and the TEAE of rash (non-erythematous) was not related to the study treatment.

Mild to moderate changes were observed for serum chemistry, and positive test results were noted for fecal occult blood and reported as mild TEAEs. None of the individual hematology, quantitative urinalysis, coagulation test values were considered clinically significant.

None of the individual vital signs were considered clinically significant or were reported as a TEAE by the investigator. No treatment-related trends were observed in 12 lead ECG measurements. One subject was reported with a mild TEAE of tachycardia that was considered clinically significant and resolved on the same day. This TEAE was considered related to the study treatment.

Phase 1 study in China (CTR20221542)

Part A (SAD)

In this study, single doses of INS018_055 (30 mg, 60 mg, 120 mg) given under fasting conditions to healthy subjects were safe and well tolerated. During the study, there were no severe adverse events, serious adverse events, adverse events leading to withdrawal from the study, or TEAEs leading to death.

A total of 24 (100.0%) subjects were included in SS, and a total of 23 TEAEs occurred to 14 (58.3%) subjects; among them, 9 TEAEs occurred to 5 (83.3%) subjects in 30 mg dose group; 2 TEAEs occurred to 2 (33.3%) subjects in 60 mg dose group; 6 TEAEs occurred to 3

(50.0%) subjects in 120 mg dose group; 6 TEAEs occurred to 4 (66.7%) subjects in placebo group.

Among subjects treated with INS018_055, the most common TEAEs were occult blood, hypertriglyceridaemia (5 subjects each, 27.8%), sinus bradycardia (2 subjects, 11.1%), and the incidences of other TEAEs were 5.6% (1 subject each). Among subjects treated with placebo, the most common TEAE was occult blood (2 subjects, 33.3%); and the incidences of other TEAEs were 16.7% (1 subject each). All TEAEs were mild in severity and recovered.

Eight (44.4%) subjects who received INS018_055 treatments had TEAEs related to the study drug, the most common TEAEs were occult blood and hypertriglyceridaemia (5 subjects each, 27.8%), and the incidence of other TEAEs was 5.6% (1 subject each); 3 (50.0%) subjects who received placebo treatment had TEAEs related to the study drug, the most common TEAE was occult blood (2 subjects, 33.3%), and the incidences of other TEAEs were 16.7% (1 subject each).

The change of any laboratory test indicator from normal/abnormal without clinical significance at baseline to abnormal with clinical significance post-dose occurred in at least 2 subjects includes: abnormally elevated triglycerides in 2 (33.3%) subjects and positive/weakly positive fecal occult blood in 3 (50.0%) subjects in the 30 mg dose group; abnormally elevated triglycerides in 2 (33.3%) subjects and positive/weakly positive fecal occult blood in 2 (33.3%) subjects in the 120 mg dose group, all were judged to be abnormal with clinical significance, and reported as TEAEs related to the study drug, these TEAEs were all recovered.

The incidence of change of any vital sign examination indicator from normal value with no clinically significant abnormality at baseline to abnormal value with clinically significance post-dose was low in each dose group, with no more than 1 (16.7%) subject. Among them, 1 (16.7%) subject in the 30 mg dose group reported diastolic blood pressure decreased as a TEAE related to the study drug, which returned to normal before the end of the study.

ECG results showed that 1 (16.7%) subject in the 30 mg dose group developed sinus bradycardia after dosing; 1 (16.7%) subject in the 60 mg dose group developed sinus bradycardia with cardiac dysrhythmias. All were judged to be abnormal with clinical significance, but not related to the study drug, and returned to normal before the end of the study.

Part B (MAD)

In this study, INS018_055 (30 mg, 60 mg, 90 mg) given twice daily for 7 days under fasting conditions to healthy subjects was safe and well tolerated. During the study, there were no severe adverse events, serious adverse events, adverse events leading to withdrawal from the study, or TEAEs leading to death.

A total of 24 (100.0%) subjects were enrolled in SS, and a total of 92 TEAEs occurred to 21 (87.5%) subjects at MAD stage; among them, 10 TEAEs occurred to 4 (66.7%) subjects in 30 mg dose group; 24 TEAEs occurred to 6 (100.0%) subjects in 60 mg dose group; 39 TEAEs occurred to 6 (100.0%) subjects in 90 mg dose group; 19 TEAEs occurred to 5 (83.3%) subjects in placebo group.

Among subjects treated with INS018_055, the most common TEAEs were occult blood (10 subjects, 55.6%), hypertriglyceridaemia (9 subjects, 50.0%), influenza like illness, pain in limb (5 subjects each, 27.8%), dizziness (4 subjects, 22.2%), rash, headache, haematuria (3 subjects each, 16.7%), blood fibrinogen decreased, white blood cells urine positive, ulceration mouth, epistaxis, fever and anaemia (2 subjects each, 11.1%), and the incidences of other TEAEs were 5.6% (1 subject each); among subjects treated with placebo, the most common TEAE were occult blood (3 subjects, 50.0%), hypertriglyceridaemia, influenza like illness and rash (2 subjects each, 33.3%), and the incidences of other TEAEs were 16.7% (1 subject each).

Except for 5 (27.8%) subjects in the INS018_055 dosing group and 2 (33.2%) subjects in the placebo group, the severity of TEAEs of influenza like illness was moderate, and the severity of other TEAEs were mild, and all TEAEs were recovered. All moderate TEAEs were not related to the study drug.
Sixteen (88.9%) subjects treated with INS018_055 had TEAEs related to the study drug, the most common TEAEs were occult blood (10 subjects, 55.6%), hypertriglyceridaemia (9 subjects, 50.0%), pain in limb (5 subjects, 27.8%), dizziness (4 subjects, 22.2%), rash, headache, haematuria (3 subjects each, 16.7%), blood fibrinogen decreased, white blood cells urine positive, ulceration mouth, epistaxis, fever and anaemia (2 subjects each, 11.1%), and the incidences of other TEAEs were 5.6% (1 subject each); 5 (83.3%) subjects treated with placebo had TEAEs related to the study drug, the most common TEAE were occult blood (3 subjects, 50.0%), hypertriglyceridaemia and rash (2 subjects each, 33.3%), and the incidences of other TEAEs were 16.7% (1 subject each).

In each dose group, the changes of laboratory test indicators from normal/abnormal without clinical significance at baseline to abnormal with clinical significance post-dose occurred in at least 2 subjects, including abnormally elevated triglycerides in 3 (50.0%) subjects in the 30 mg dose group; abnormally elevated triglycerides in 4 (66.7%) subjects and positive/weakly

positive fecal occult blood in 4 (66.7%) subjects in the 60 mg dose group; abnormally decreased haematocrit, hemoglobin, red blood cell count, and serum sodium in 2 (33.3%) subjects, abnormally decreased lymphocyte percentage and lymphocyte count in 4 (66.7%) subjects, abnormally elevated triglycerides in 2 (33.3%) subjects and positive/weakly positive fecal occult blood in 5 (83.3%) subjects in the 90 mg dose group; abnormally elevated triglycerides in 2 (33.3%) subjects and positive/weakly positive fecal occult blood in 3 (50.0%) subjects in the placebo group, all were judged to be abnormal with clinical significance. Except for 1 subject (01-175) with abnormally decreased serum sodium in the 90 mg dose group, the rest of the abnormal changes were reported as TEAEs related to the study drug, and all these TEAEs were recovered.

In each dose group, the changes of vital sign examination from normal/abnormal without clinical significance at baseline to abnormal with clinical significance post-dose occurred in at least 2 subjects, including body temperature increased in 6 (100.0%) subjects, diastolic blood pressure decreased in 3 (50.0%) subjects, and pulse increased in 2 (33.3%) subjects in the 90 mg dose group, all were judged to be abnormal with clinical significance. One (16.7%) subject in each of the 30 mg, 60 mg, 90 mg and placebo groups reported 1 TEAE related to the study drug, which returned to normal before the end of the study.

Physical examination results showed that 1 (16.7%) subject in each of the 30 mg dose group, 60 mg dose group, and placebo group and 4 (66.7%) subjects in the 90 mg dose group had abnormal change with clinical significance, all of which were reported as TEAEs related to the study drug and returned to normal/abnormal without clinical significance before the end of the study.

ECG test results showed that 1 (16.7%) subject in the 30 mg dose group developed sinus bradycardia; 2 (33.3%) subjects in the 90 mg dose group developed sinus tachycardia; 1 (16.7%) subject in the placebo group developed sinus bradycardia with cardiac dysrhythmias, all were judged to be abnormal with clinical significance. Among them, 1 (16.7%) subject each in the 30 mg and placebo groups reported a TEAE related to the study drug, which returned to normal before the end of the study.

In summary, in this Phase 1 study conducted in healthy subjects, no severe adverse events or serious adverse events were observed after single oral-route dose of INS018_055 Capsules at 30-120 mg or multiple oral-route doses of INS018_055 Capsules at 30-90 mg for 7 consecutive days (Q12 h), indicating good safety and tolerability of INS018_055 Capsules.

1.3 RATIONALE FOR PERFORMING THE STUDY

There is an unmet need in IPF for novel treatments that further slow disease progression and expand treatment options for patients unable to tolerate currently approved treatments. New

treatments that further reduce decline in FVC, positively affect symptoms, and improve QoL would fill this gap. [Chambers 2022] [Somogyi 2019]

In pre-clinical studies, INS018_055 potently inhibited TGF-β-induced expression of fibrotic markers, such as α-SMA, fibronectin, PAI-1 and collagen I in MRC-5 cells (a lung fibroblast cell line), or primary lung fibroblasts, primary bronchial epithelial cells derived from IPF patients or other cell lines. In *in vivo* studies performed with a BLM-induced lung fibrosis mouse model, all INS018_055 treated groups (3 mg/kg BID, 10 mg/kg BID, or 30 mg/kg BID) showed improved lung function by significantly lowered Penh, i.e., enhanced pause, an indicator of bronchoconstriction (higher value indicates more difficulty breathing). Both anti-fibrotic and anti-inflammatory effects were also observed. Furthermore, the anti-inflammatory effect was further validated in LPS-induced acute lung injury mouse model, which indicate INS018_055 may benefit patients with IPF, a complex progression involves both fibrosis and inflammation.

In one combination therapy study in BLM-induced lung fibrosis mouse models, INS018_055 showed additive effects with subtherapeutic dose of pirfenidone. In a second combination therapy study, combination INS018_055 with optimal dose of pirfenidone showed improvement in clinical observations and lung function, [redacted]. In phase 1 studies, these preliminary data from healthy subjects demonstrates that INS018_055 is well tolerated with manageable side effects.

This phase IIa proof-of-concept (PoC) study will investigate the safety and tolerability of INS018_055 at three doses (30 mg QD, 30 mg BID, 60 mg QD) on change in FVC from baseline through 12 weeks of treatment compared to placebo. The safety and PoC of clinical activity of INS018_055 from the overall study population will be used to inform the phase 3 program.

1.4 BENEFIT-RISK ASSESSMENT

1.4.1 Potential Benefits

BLM-treated mice showed an increased Penh, i.e., enhanced pause, an indicator of bronchoconstriction (higher value indicates more difficulty breathing) as determined by whole-body plethysmography. This effect was reduced by INS018_055 (orally administered BID) at all doses tested: significantly decreased total cell numbers (3 mg/kg BID, 10 mg/kg BID, and 30 mg/kg BID), monocyte numbers (10 mg/kg and 30 mg/kg), and neutrophil numbers (3 mg/kg BID, 10 mg/kg BID, and 30 mg/kg BID) in bronchoalveolar lavage fluid (BALF); IL-1β, IL-6 and TGF-β1 levels and soluble collagen (3 mg/kg BID, 10 mg/kg BID, and 30 mg/kg BID) in BALF; the expression of Col1α1, Col1α3, and PAI-1 in the lung (3

mg/kg BID, 10 mg/kg BID, and 30 mg/kg BID); lung inflammation areas, modified Ashcroft scores and lung fibrosis areas, positive α-SMA and collagen I staining areas in the lung (3 mg/kg BID, 10 mg/kg BID, and 30 mg/kg BID) compared to the model group, i.e. BLM group without treatment.

Combination INS018_055 with [redacted]/pirfenidone dosed sub-therapeutically was studied in a BLM-induced mouse lung fibrosis model. [redacted]. Combination INS018_055 3 mg/kg BID with pirfenidone 60 mg/kg BID showed greater anti-inflammatory and anti-fibrotic effects than with either compound alone. Combination INS018_055 3 mg/kg BID with pirfenidone 60 mg/kg BID was the only treatment that significantly reduced the neutrophil number in BALF, the inflammation area in the lung, and the expression of surfactant protein A.

In a second combination therapy study, INS018_055 10 mg/kg BID with optimal therapeutic dose of pirfenidone 200 mg/kg BID showed significantly improved lung function and was better than any of the monotherapies. This combination therapy group also exhibited the greatest recovery of body weight loss.

Animals from vehicle-treated BLM model groups were observed to have hunching or hypokinesia, which was less frequent and affected fewer animals treated with monotherapies (INS018_055 or pirfenidone alone) and the combination therapies (INS018_055 1 mg/kg BID or 3 mg/kg BID; pirfenidone 200 mg/kg BID). This was not observed in the combination therapy group (INS018_055 10 mg/kg BID / pirfenidone 200 mg/kg BID). [redacted]

INS018_055 was also validated for anti-inflammation in an LPS-induced acute lung injury model in mice. Compared to the vehicle-treated model group, INS018_055 dosed at 3 mg/kg BID or 10 mg/kg BID (one dose before and one dose after the challenge by LPS) significantly decreased the levels of IL-1α, IL-1β, IL-6, IL-7, IL-17A, TNF-α, TGF-β, MCP-1, MIP-1α in BALF. INS018_055 3 mg/kg BID also significantly reduced the level of myeloperoxidase (MPO) in lungs. Compared to the vehicle-treated model group, INS018_055 6 mg/kg QD or 20 mg/kg QD (single dose after the challenge by LPS) significantly decreased total cell numbers, lymphocyte, and neutrophil numbers in BALF, decreased IL-1α, IL-1β, IL-6, IL-7, IL-17A, TNF-α, TGF-β, MCP-1, MIP-1α in BALF, and

MPO in the lung. All INS018_055 groups showed significant increase in IL-4 and IL-10 in BALF compared to LPS-only treatment in the model group.

IPF is a complex disease that involves both fibrosis and inflammation. These pre-clinical results indicate that INS018_055 may benefit patients with IPF. To date, the clinical data show that INS018_055 has a manageable safety profile with mild and transient AEs. This phase IIa study will help gain further insight into the effect that INS018_055 orally administered at select doses has on safety and tolerability, and potentially early efficacy on lung function (FVC decline) and QoL. Overall, INS018_055 is anticipated to be safe and well tolerated and would represent a new treatment option in IPF.

1.4.2 Potential Risks

For all risks of clinical relevance, the mitigation strategy includes following management strategies as described in approved labels as well as allowing for investigator-determined treatment interruption and/or discontinuation.

Table 3. Risks of Clinical Relevance

Risks (possible/known) of Clinical Relevance*	Rationale for Risk	Mitigation Strategy
Investigational Product INS018_055		
Safety with SoC antifibrotic treatments	At the start of this12-weeks treatment trial, no safety data will be available for INS018_055 given concurrently with marketed SoC antifibrotics (pirfenidone, nintedanib)	-Data safety monitoring board (DSMB) will ongoingly assess the entire safety data
GI disorders, e.g., diarrhea, nausea, vomiting, abdominal pain	Constipation and positive FOBT were reported in the preliminary results of the phase 1 study (NCT05154240)	-Increased awareness of GI disorders -Careful monitoring of hydration for diarrhea
Neurological symptoms	Headache, lightheadedness, and altered sensation were reported in the preliminary results of the phase 1 study (NCT05154240).	-Increased awareness and monitoring for worsening symptoms
Hair loss	Hair loss was reported in the preliminary results of the phase 1 study (NCT05154240)	-Increased awareness and monitoring

Reproductive toxicity	Specific studies to evaluate the potential for INS018_05518 to affect fertility and developmental toxicity have not yet been conducted	-Exclusion of pregnant or lactating women -Pregnancy testing at each study visit -Agreement by study subjects to use acceptable contraception during the study
Elevated AST/ALT	Elevated AST/ALT was reported in the preliminary results of the phase 1 study (NCT05154240)	-Increased awareness and monitoring -LFTs will be drawn at each study visit
Elevated Triglycerides	Elevated triglycerides were reported in the preliminary results of the phase 1 study (CTR20221542)	-Increased awareness and monitoring -Lipid panel will be drawn at each study visit
Study Procedures		
PK interaction with moderate/strong CYP3A4 inhibitors/inducers or medications primarily metabolized by CYP3A4	Based on *in vitro* data, INS018_055 is primarily metabolized (80%) by CYP3A4. Concomitant use of INS018_055 and moderate/strong CYP3A4 inhibitors or inducers could change the exposure of INS018_055. Study allows for subjects to continue background SoC antifibrotic therapy, including nintedanib. Concomitant use of nintedanib and a CPY3A4 inhibitor/inducer may change the exposure of nintedanib.	-Exclusion of subjects taking medications known to be moderate/strong CYP3A4 inhibitors or inducers, or medications primarily metabolized by CYP3A4 -Exclusion of subjects who have consumed grapefruit, grapefruit juice, pomelo, Seville orange, Seville orange-containing products juice within 48 hours before Day 1 -Exclusion of subjects who have consumed St. John's Wort within 1 week before Day 1 [Imai 2008]
PK interaction with strong CYP1A2 inhibitors/inducers or medications primarily metabolized by CYP1A2	Study allows for subjects to continue background SoC antifibrotic therapy, including pirfenidone. Concomitant use of pirfenidone and a	-Exclusion of subjects taking medications known to be CYP1A2 inhibitors or inducers, or medications primarily metabolized by CY1A2

	strong/moderate CYP1A2 inhibitor/inducer may change the exposure of pirfenidone.	
High Resolution Computed Tomography Scan (HRCT)	HRCT is required to confirm diagnosis of IPF	-HRCT is needed in the absence of a historical HRCT performed within 12 months before Screening (Visit 1) or if the historical HRCT is of inadequate quality -When HRCT is needed, there will be close monitoring of AEs, selection of site based on ability to perform HRCT and ability of staff to conduct correct procedure
Administration of Placebo	No treatment benefit	-Thorough informed consent -Inclusion in protocol that subjects not on SoC treatments are eligible if they have discussed with their physician all available SoC therapies prior to enrollment

*See **Abbreviations** as needed

1.4.3 Discussion

Current understanding of the mode of action of INS018_055 – specifically, its TNIK inhibitory activity affecting the Wnt signaling pathway, which has been shown to significantly contribute to the pathogenesis of lung fibrosis – suggests that INS018_055 has the potential to yield meaningful benefit to patients with IPF by slowing decline of lung function as well as improving symptoms and quality of life (QoL). INS018_055 has potential to be a new therapy for patients with IPF, particularly those with limited treatment options, i.e., intolerance to currently available therapies.

Overall, the preliminary results from the phase 1 study in NZ (NCT05154240) showed that INS018_055 orally administered at a single dose of 10 mg, 30 mg, 60 mg, 90 mg, or 120 mg

(SAD) and dosed at 30 mg QD, 60 mg QD, or 120 mg QD for up to 7 days (MAD) appears to have a manageable safety profile.

The currently available PK data of INS018_055 showed a dose-proportional increase in plasma exposure from 10 mg to 120 mg in SAD cohorts and no significant accumulation after 7-day once daily oral administrations when the steady state was reached. Food effect led to approximately 38% of decrease in C_{max} and 14% of decrease in AUC under fed conditions compared to fasted conditions based on data with the same dose level in the same set of subjects. Median T_{max} shifted from 1 hour to 3 hours post-dose. These studies support the initiation of this randomized, parallel-group study to evaluate the safety, tolerability, PK, and PoC for efficacy of INS018_055 administered orally to patients with IPF. In this phase IIa study, INS018_055 administered at three doses, 30 mg QD or 30 mg BID or 60 mg QD (maximum 60 mg daily), is considered appropriate from both a pre-clinical and clinical point of view.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Primary Objective

The primary objective is to evaluate the safety and tolerability of INS018_055 orally administered for up to 12 weeks in adult subjects with IPF compared to placebo.

2.1.2 Secondary Objectives

The secondary objectives are:

- To evaluate the pharmacokinetics of INS018_055 orally administered to subjects with IPF
- To evaluate the efficacy of INS018_055 orally administered for up to12 weeks of treatment on FVC decline in adult subjects with IPF compared to placebo
- To evaluate the efficacy of INS018_055 orally administered for up to12 weeks of treatment to improve quality of life (QoL) and functional measures compared to placebo
- To evaluate the impact of INS018_055 orally administered on acute IPF exacerbations compared to placebo

2.1.3 Primary Endpoint

The primary endpoint is the percentage of patients who have at least 1 treatment-emergent adverse event (TEAE). An AE will be counted irrespective of treatment compliance, early treatment discontinuation, or use of antifibrotic or prohibited therapies. Similar estimates for specific serious AEs (SAEs), TRAEs, AEs of special interest (AESIs) and abnormal clinical findings may be specified in the statistical analysis plan (SAP).

2.1.4 Secondary Endpoints

The secondary endpoints are:

- PK parameters of INS018_055 and metabolites (INS018_063 and INS018_095) following the first dose on Day 1 (Visit 2) and the last dose during Week 12 (Visit 6, EOT):
    - Maximum plasma concentration (C_{max})
    - Time at which the maximum plasma concentration occurred (t_{max})
    - Area under the plasma concentration-time curve from time zero to:
        - Dosing interval τ ($AUC_{0-\tau}$)
        - Time with last measurable concentration t (AUC_{0-t})
        - Infinity (∞) (AUC0-∞)

- Terminal elimination half-life ($t_{1/2}$)
- Terminal elimination rate constant (λz)
- Apparent clearance (CL/F)
- Apparent volume of distribution (Vz/F)
- Accumulation ratio (Rac) for C_{max} and AUC
- Trough plasma concentration (C_{trough}).

- Relative change in FVC in mL from Week 0/Visit 2 up to Week 12
- Percentage change in FVC in mL from Week 0/Visit 2 up to Week 12
- Absolute and relative change in FVC % predicted from Week 0/Visit 2 up to Week 12
- Change in Diffusion Capacity of the lung for Carbon Monoxide (DLCO) % predicted from Week 0/Visit 2 to Week 12
- Change in Leicester Cough Questionnaire (LCQ) from Week 0 to Week 4, 8 and 12
- Change in 6-Minute Walk Distance (6MWD) in meters, from Week 0 to Week 12
- Number of acute IPF exacerbations from Week 0 up to Week 12
- Number of days hospitalized for acute IPF exacerbations from Week 0 to up Week 12

2.2 EXPLORATORY OBJECTIVES AND EXPLORATORY ENDPOINTS

2.2.1 Exploratory Objective

The exploratory objective is:

- To explore the impact of oral INS018_055 on IPF disease-related biomarkers in the blood
- To explore the potential mechanism of action of INS018_055 in IPF patients by high-throughput proteomic analysis on blood proteome

2.2.2 Exploratory Endpoint

The exploratory endpoint is:

- Change in IPF blood biomarkers upon INS018_055 treatment from Week 0 to Weeks 2, 4, 8 and 12.
- Change in blood proteome in IPF patients upon INS018_055 treatment from Week 0 to Weeks 2, 4, 8 and 12.
-

3 DESCRIPTION OF STUDY DESIGN AND STUDY POPULATION

3.1 OVERALL STUDY DESIGN

This is a randomized, double-blind, placebo-controlled, parallel-group, PoC phase IIa study evaluating safety/tolerability, PK, and efficacy of INS018_055 orally administered at three doses, 30 mg QD or 30 mg BID or 60 mg QD (maximum 60 mg daily). Patients randomized into the study will be treated for 12 weeks.

After providing informed consent, subjects will undergo a screening visit (Visit 1) up to 30 days prior to the first day of the treatment period (Day 1, Visit 2). Subjects on SoC treatment for IPF with nintedanib or pirfenidone will be eligible for study enrollment and to continue receiving their nintedanib or pirfenidone throughout the study. Eligible subjects who meet all inclusion criteria and no exclusion criteria will be assigned in a 1:1:1:1 ratio to 1 of 4 treatment arms:

- INS018_055 30 mg QD
- INS018_055 30 mg BID
- INS018_055 60 mg QD
- Placebo

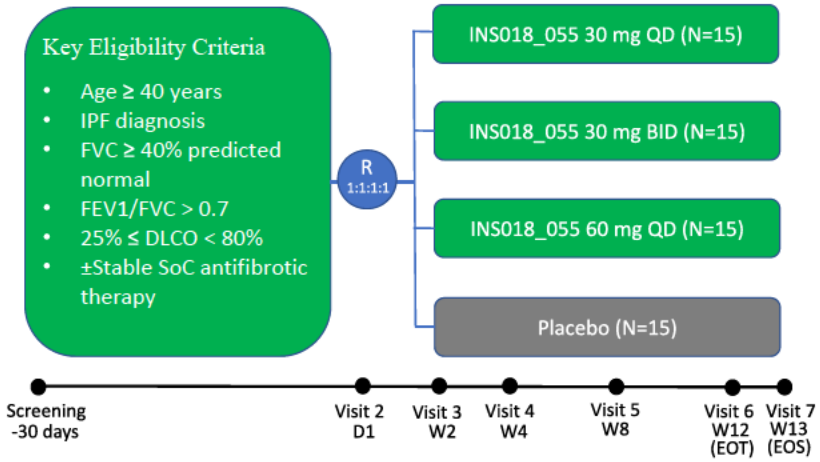
A target of 15 subjects will be assigned to each treatment arm. Approximately 70 patients will be enrolled to ensure approximately 60 patients complete treatment of 12 weeks. Subjects being treated with background SoC antifibrotic therapy (nintedanib or pirfenidone) at the time of randomization will be maintained on their therapy throughout the study.

The duration of the study will be approximately 17 weeks for each subject from Visit 1 through the Visit 7 (EOS). The treatment period will include 5 visits: Study Day 1, 15 ± 3 (Week 2), 29 ± 7 (Week 4), 57 ± 7 (Week 8), and 85 ± 7 (Week 12, EOT). Subjects will return for an EOS visit approximately 1 week after completing the treatment period (Visit 7).

Following the Schedule of Study Activities, all visits [Visit 1-7 (EOS)] will include a physical exam, vital signs, weight, laboratory tests, urinalysis, medication review, assessment for AEs, and pregnancy testing (WOCBP). During the treatment period, subjects will also be assessed for COVID-19, BMI, ECG, study drug compliance, blood sampling [PK (study drug, SOC antifibrotic therapy), biomarker, LCQ, spirometry, DLCO, 6MWD, and acute IPF exacerbations. Safety will be assessed from Visit 1 through the follow-up visit at Week 13 (Visit 7, EOS). Efficacy assessments will occur through Week 12 (Visit 6).

Study sites will dispense INS018_055 at each study visit starting with Visit 2. Subjects will also receive placebo at each study visit to maintain blinding. Subjects will orally self-administer their assigned treatment for 12 weeks [until Week 12; Visit 6 (EOT)]. Sites will instruct subjects about treatment schedule, study diary, and return of all study medications at each visit. Sites will also follow up with patients to ensure correct self-administration. Subjects will return for a follow-up visit approximately 1 week after completing the treatment period [Visit 7; end of study (EOS)]. In case of early treatment discontinuation, subjects are expected to follow the trial schedule as per protocol.

Figure 1. Study Schema



BID = twice daily dosing, EOS = end of study; EOT = end of treatment, QD = daily dosing, R = randomized, SOC = standard of care, W = week

3.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

Two phase 1 studies in New Zealand (NCT05154240) and China (CTR20221542) in healthy subjects showed INS018_055 has a manageable safety profile; the majority of TEAEs are mild and transient. Clinical study reports for both phase 1 studies are available.
This study is a randomized, double-blind, placebo-controlled, parallel-group study designed to yield the most robust results based on what is known to date about INS018_055 and the IPF treatment landscape. Therefore, this study is considered the most appropriate design. A randomized design allows for rigorous assessment of intervention/outcome cause/effect

relationship. A double-blind design minimizes bias, and a parallel-group design is best for efficiency and cost effectiveness.

In this study, subjects not on SoC treatments are eligible if they have discussed with their physician all available SoC therapies prior to enrollment. The use of placebo may raise ethical concerns since SoC treatment includes antifibrotic treatment. [Richeldi 2014] [Flaherty 2019] [Temple 2000] [Krishna 2022. However, the response to antifibrotic treatment may be limited by side effects and intolerance. [Galli 2017] [Strens 2021] Moreover, SoC antifibrotics such as nintedanib and pirfenidone can slow progression of IPF but do not significantly impact mortality. [Somogyi 2019] [Maher 2019]

A treatment duration of 12 weeks will inform the safety and tolerability of INS018_055 overall and at 3 different doses in patients with IPF. This treatment period approximates or exceeds that of treatment periods in related studies. [Oguro 2015] [Richeldi 2014] In addition, a 12-week treatment duration will provide insight into the PK profile of INS018_055, potential early efficacy for FVC decline, and improvement in QoL.

A DSMB will assess safety and tolerability during the study by evaluating entire safety data on an ongoing basis. FVC was chosen as a clinical endpoint, since it is a reliable, valid, and responsive measure of clinical status of IPF. [du Bois 2011] Lung function and respiratory symptoms are also clinically meaningful outcomes [Raghu 2022], thus 6MWD, number of acute IPF exacerbations, number of days hospitalized for IPF exacerbations, and patient-reported QoL (LCQ) are also included as clinical endpoints. [Raghu 2022]

In this PoC study, the testing of selected doses for INS018_055 orally administered is guided by phase 1 studies (NCT05154240, CTR20221542). The selected doses of 30 mg QD, 30 mg BID, or 60 mg QD will provide insight into comparative safety and efficacy across different doses and versus placebo.

A formal sample size calculation based on statistical power considerations will not be performed. Further details about the statistical approach, including rationale for sample size, is described in the Statistical Analysis Plan.

3.3 SELECTION OF STUDY POPULATION

This Phase IIa study will include patients with IPF with and without background SoC antifibrotic therapy (nintedanib or pirfenidone). Determination of study criteria was guided

by studies of other therapies studied in IPF [Oguro 2015] [Richeldi 2014] and consultation with pulmonologists.

This study will aim to assign15 patients in each treatment arm. Approximately 70 patients will be enrolled to ensure approximately 60 patients complete treatment of 12 weeks. All patients enrolled into the study must meet all inclusion criteria (section 3.3.2) and no exclusion criteria (section 3.3.3) as outlined, respectively.

Subjects being treated with nintedanib or pirfenidone at the time of randomization will be maintained on their respective therapy throughout the study. The 1:1:1:1 randomization scheme will eliminate selection bias, allow for balanced allocation, and contribute to internal study validity.

The screening period will be 30 days during which subject eligibility will be evaluated. If a patient is unable to complete the necessary study procedures due to unforeseen circumstances or because of the need for retesting, the screening period can be extended by a maximum of 2 weeks for a total allowed screening time of 44 days.

A sufficient number of male and female patients with a confirmed diagnosis of IPF will be screened to meet the study enrollment goal. Screening for this study is competitive. Screening will simultaneously cease at all study sites once a sufficient number of patients has been screened. At the time of this notice, subjects who are currently in screening will be permitted to continue to study enrollment if they are determined to be eligible.

Documentation of screening results, including number of subjects screened, number of subjects who meet study criteria, number of subjects who do not meet study criteria, and reason for screen failure, will be captured in the Investigator Site File (ISF). A log of all subjects enrolled into the study, defined as having signed and dated informed consent, will be maintained regardless of the subject's status of taking INS018_055. If a patient is enrolled in error, such as not meeting all inclusion criteria or meets any exclusion criteria on the day of enrollment, the sponsor should be contacted immediately.

3.3.1 Main Diagnosis for Study Entry

Subjects who have a diagnosis of IPF, meet all inclusion (section 3.3.2) and no exclusion criteria (section 3.3.3) are eligible to be enrolled in the study. Please refer to Source Documents (section 8.3.1) for the documentation requirements pertaining to the inclusion criteria and exclusion criteria.

3.3.2 Inclusion Criteria

1. Informed consent signed and dated at screening visit, prior to initiation of any study related procedures, and in accordance with ICH-GCP and local legislation
2. Subjects aged ≥ 40 years at time of signing informed consent
3. Diagnosis of IPF confirmed by investigator and according ATS/ERS/JRS/ALAT Clinical Practice Guideline. The current ATS/ERS/JRS/ALAT Clinical Practice Guideline at the time of diagnosis should be referenced, i.e., 2022
    a. Diagnosis must be confirmed by HRCT scan. HCRT scan must be performed within 12 months prior to screening and, if available, surgical lung biopsy. If an HRCT scan within 12 months prior to screening is not available, a scan to qualify for study eligibility may be performed during the screening period. If HRCT is equivocal, surgical lung biopsy results may be used.
4. Maintenance of ADL with supplemental oxygen up to a maximum of 6 L/min is allowed
5. Ability to walk ≥ 150 meters during the 6MWD at Visit 1. Supplemental oxygen up to 6 L/min may be added
6. FVC ≥ 40% predicted normal at Visit 1 as confirmed through central review
7. Absence of relevant airway obstruction defined as prebronchodilator FEV1/FVC ratio > 0.7 (Tiffeneau-Pinelli index) at Visit 1 as confirmed through central review
8. Diffusing capacity of lung for carbon monoxide (DLCO) corrected for hemoglobin ≥ 25% and < 80% predicted normal at Visit 1
9. Subjects with background pirfenidone or nintedanib may be enrolled if their regimen of antifibrotic therapy has been stable for ≥ 8 weeks prior to Visit 1
10. Subjects who were previously treated with pirfenidone or nintedanib and discontinued this treatment may be enrolled if it has been ≥ 4 weeks since they discontinued this treatment and there is no plan for them to restart this treatment during the study
11. Subjects who have never received SoC treatment pirfenidone or nintedanib are eligible to participate if they meet all other study eligibility criteria and have discussed all SoC treatment options with their physician

12. Subjects must agree to use acceptable contraceptive methods during the study to avoid pregnancy, from first dosing day (Visit 2, Day 1) until 3 months after study completion (Visit 7, EOS):
    a. Female subjects of childbearing potential must have a negative pregnancy test result at Visit 1
    b. Female subjects not of childbearing potential, defined as > 6 weeks after hysterectomy with or without surgical bilateral oophorectomy, or postmenopausal (> 12 months since natural amenorrhea) are not required to have a negative pregnancy test at Visit 1. In questionable cases, a blood sample with simultaneous levels of follicle-stimulating hormone (FSH) > 40 U/L and estradiol < 30 ng/L is confirmatory
    c. Male subjects with partners of childbearing potential must agree to use acceptable contraceptive methods during the study to avoid pregnancy in their female partners from first dosing day (Visit 2, Day 1) until 3 months after study completion (Visit 7, EOS)
    d. Acceptable methods of contraception include: barrier contraception and a medically accepted contraceptive method for the female partner (intrauterine device with spermicide, hormonal contraceptive used for $\geq$ 2 months prior); true sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject); or surgically sterilized, including vasectomy for men. Women not of childbearing potential do not need to follow any contraceptive method

3.3.3 Exclusion Criteria

1. Presence of other clinically significant airway disease that may, in the opinion of the investigator, impact the study safety or efficacy objectives, such as cystic fibrosis, active aspergillosis, active tuberculosis, or other serious concomitant respiratory disorder other than pulmonary fibrosis. Investigators are encouraged to discuss eligibility of subjects with respiratory diagnoses other than IPF with the medical monitor before study enrollment if there is uncertainty over the potential to impact study outcomes
    a. Subjects with emphysema or asthma may be included if fibrosis is the major contributing factor to the subject's respiratory disorder upon HRCT central overread.
    b. Subjects with comorbid emphysema or asthma may be eligible if all the following are true:

   i. Receiving ≤ 2 controller therapies (2 different mechanisms of action) and no changes to their controller regimen within 3 months before dosing (Day 1)
   ii. No disease exacerbation that required systemic corticosteroids or hospitalization within the past 12 months before dosing (Day 1)
   iii. Stable comorbid disease in the opinion of the investigator
   iv. Extent of emphysema on CT scan does not exceed the extent of fibrotic changes as assessed by investigator review of HRCT and all other entry criteria (e.g., FEV1/FVC > 0.7) are met upon central overread
2. Subjects with contraindications for forced expiratory maneuvers during pulmonary function testing
3. Coronavirus disease (COVID-19):
   a. Confirmed COVID-19 infection at Visit 1 or at Visit 2, either by reverse transcription polymerase chain reaction test or by rapid antigen test
      i. Subjects who previously had a positive COVID-19 test result at Visit 1 or Visit 2 may be reconsidered for study enrollment after they recover from the infection as confirmed by a negative retest before enrollment
   b. History of severe COVID-19 infection requiring hospitalization within the last 6 months prior to Visit 1
   c. History of Long COVID-19, defined as symptoms beyond 12 weeks of acute infection, that has not fully resolved prior to Visit 1
   d. COVID-19 vaccine within 7 days before Visit 2 (Dosing day 1). Any systemic symptoms, e.g., myalgia, fever, chills, fatigue, after COVID-19 vaccine should have subsided ≤ 2 days before Visit 2
4. Pulmonary hypertension that is clinically relevant or severe as deemed by the investigator
5. Acute IPF exacerbation within 4 months prior to Visit 1 and/or during the screening period, as determined by the investigator
6. Upper or lower respiratory tract infection that has not fully resolved within 4 weeks prior to Visit 1 and/or before Visit 2 (Day 1). Patients who have had an upper or lower respiratory tract infection within 4 weeks prior to Visit 1 and/or before Visit 2 (Day 1) may be rescreened once they have recovered in the opinion of the investigator
7. Subject is active on the lung transplantation register or expected to become active on the lung transplant register within 6 months prior to Visit 1 based on the opinion of the investigator. Patients who were previously assessed for lung transplantation are eligible if they are not actively waiting for a transplant
8. Subject has a history of lung volume reduction surgery or lung transplant

9. Current smoker. All inhaled products, including cigarettes, pipes, cigars, e-cigarettes/ vaping, and marijuana, are prohibited throughout the study. Prior smokers are eligible if they have not used any nicotine- or tobacco-containing products for ≥ 3 months prior to Visit 1
10. BMI > 40 kg/m^2
11. Subjects with AST or ALT ≥ 1.5 times ULN or total Bilirubin ≥ 1.5 times ULN at Visit 1
12. eGFR ≤ 60 $mL/min/1.73m^2$ (CKD-EPI formula) at Visit 1
13. Subjects with uncontrolled hypertension (systolic pressure > 160 mmHg or diastolic pressure > 95 mmHg despite treatment with anti-hypertensive treatments) at Visit 1. Sites may repeat the blood pressure measurement once after ≥ 10 minutes and use the lower values to determine eligibility
14. Subjects with unstable cardiac angina or myocardial infarction within 6 months prior to Visit 1
15. Subjects taking oral corticosteroids at a daily dose of >15 mg prednisone or equivalent, combination of prednisone, azathioprine, and N-acetylcysteine, ambrisentan, or imatinib within 30 days prior to Visit 2
16. Subjects with any documented active or suspected malignancy or history of malignancy within 5 years prior to Visit 1, except appropriately treated basal cell carcinoma of the skin, in situ carcinoma of the uterine cervix, or prostate cancer under surveillance that are considered cured, inactive, and/or not currently under treatment.
17. Subjects with known hypersensitivity or contraindications to serine/threonine kinase inhibitors (including but not limited to the following FDA-approved kinase inhibitors such as Abemaciclib, Belumosudil, Dabrafenib, Encorafenib, Everolimus, Netarsudil, Palbociclib, Ribociclib, Sirolimus, Temsirolimus, Trilaciclib and Vemurafenib, etc) [Roskoski 2023].
18. Subjects with any condition or treatment possibly affecting drug absorption, e.g., gastrectomy, metoclopramide
19. Significant trauma or major surgery within 3 months prior to Visit 1, or planned major surgery during the study
20. Subjects taking restricted medications, e.g., moderate/strong CYP3A4/CYP1A2 inhibitors/inducers or medications primarily metabolized by CYP3A4/CYP1A2, or who have consumed grapefruit or grapefruit juice, pomelo, Seville orange or Seville orange-containing products juice within 48 hrs before Day 1 [for St. John's Wort: within 1 week before Day 1 (Imai 2008)], all of which are considered likely to interfere with safe conduct of the study

21. Subjects who are currently enrolled or have previously participated in interventional clinical studies within 30 days or 5 half-lives of investigational therapy (whichever is longer) prior to Visit 1
22. Subjects with other medical or psychological condition, which in the opinion of the investigator and/or medical monitor, might create undue risk to the subject, interfere with subjects' compliance to the protocol requirements, or affect subjects' ability to compete the study
23. Subjects who are pregnant or lactating
24. Subjects with active alcohol or drug abuse, in the opinion of the investigator
25. Subjects with underlying chronic liver disease (Child Pugh A, B or C)
26. Subjects with positive human immunodeficiency virus (HIV) or positive for hepatitis B surface antigen (HBsAg) or positive for HCV antibody (HCVAb) or positive for specific treponema pallidum antibody or positive for syphilis will be excluded
    a. HBV positive is defined as HBsAg positive or HBcAb positive＋HBV DNA positive. HBcAb positive＋HBV DNA negative is allowed
    b. HCV positive is defined as HCV antibody positive＋HCV RNA positive. HCV antibody positive＋HCV RNA negative is allowed
    c. HIV positive is defined as HIV antibody positive.
27. Subjects with evidence of active infection (chronic or acute) based on clinical exam or laboratory findings at Visit 1 or Visit 2
28. The subject has 12-lead ECG demonstrating corrected QT interval by Fridericia (QTcF) > 450 msec for males and > 470 msec for females, or a QRS interval > 120 msec at Visit 1. If these parameters are met at first take, the ECG should be repeated 2 more times. The average of the 3 QTcF (or QRS interval) values should be used in that case to determine the subject's eligibility
29. Subjects with a significant disease or condition (other than IPF) which, in the opinion of the investigator, may put the subject at risk because of participation, interfere with study procedures, or cause concern regarding the subject's ability to participate in the study
30. Subjects with any medical condition that leads to a life expectancy < 12 months
31. Previous randomization in this study

3.3.4 Withdrawal of Subjects From Treatment or Assessments

Patients may discontinue study treatment or withdraw consent to study participation as a whole ("withdrawal of consent") with very different implications. For additional details, see section 3.3.4.1 and section 3.3.4.2.

Every effort should be made to keep the subjects enrolled in the study. If possible, subjects will stay on study treatment, or at least continue to collect important study data. Subjects who choose to withdraw from the study will have an EOT visit within 7 days according to the Schedule of Assessments. Strategies to control the withdrawal rate include careful subject selection, clear informed consent including appropriate and thorough explanation of study requirements and procedures prior to study enrolment, as well as explanation of the consequences of study withdrawal. Investigators are encouraged to discuss a subject's withdrawal with the medical monitor prior to deciding to discontinue.

The decision to discontinue trial treatment or withdraw consent to study participation and the reason for either of these decisions must be documented in the patient files and eCRF. If applicable, consider the requirements for Adverse Event collection reporting (5.6.4)

3.3.4.1 Discontinuation of Study Treatment

A subject enrolled in the study will be considered to discontinue study treatment if:

- The subject indicates wanting to discontinue study treatment, without the need to justify this decision
- The subject is shown to be repeatedly non-compliant with important study procedures. In addition, the investigator and sponsor representative determine that the subject is not willing or unable to adhere to future study requirements
- The subject experiences unacceptable adverse events in the opinion of the investigator
- The subject needs to take concomitant medication(s) that interfere with the investigational medicinal product or other study treatment (4.2.2) and would constitute a safety hazard
- The subject can no longer receive study treatment for medical reasons, such as surgery, adverse events, other diseases, or pregnancy.
- For subject with BMI < 18.5 kg/m^2 at Visit 2 only: unexplained and clinically significant weight loss (> 10%)
- The subject has clinically relevant changes in ECG requiring intervention
- The subject has QTcF > 500 ms in ECG

In case of a temporary reason, trial treatment should be restarted if medically justified. Investigator should consult with the medical monitor. If new efficacy/safety information becomes available, InSilico Medicine will review the benefit-risk profile of INS018_055. If

warranted, there may be pausing or stopping of study treatment or taking other appropriate action to guarantee the safety of study patients. If study treatment is discontinued, if possible, subjects should follow the study schedule as outlined in the Schedule of Study Activities to complete the subsequent visits.

3.3.4.2 Withdrawal of Consent to Study Participation

Subjects may withdraw their consent to study participation at any time without the need to justify the decision. If a subject wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between study treatment discontinuation and withdrawal of consent to study participation. In addition, the investigator should explain the options for continued follow-up after study treatment discontinuation as described in section 6.4.

3.3.4.3 Discontinuation of Study by the Sponsor

InSilico Medicine reserves the right at any time to discontinue the study overall or at a specific study site for the following reasons:

1. Failure to meet expected enrollment goals
2. New efficacy or safety information about INS018_055 invalidating the earlier positive benefit-risk-assessment (section 1.4)
3. Deviations from GCP, study protocol, or the contract impairing the appropriate conduct of the study

In the case of sponsor-determined study termination, further follow up of subjects will occur as described in section 6.4. InSilico Medicine will work with the investigator and study site to reimburse for reasonable expenses incurred and related to reasons 1 and 2 above.

4 TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Study treatments, INS018_055 and placebo, will be manufactured by a qualified vendor.

4.1.1 Identity of Investigational Medicinal Products

The characteristics of the medicinal products are shown in Table 4.

Table 4. Characteristics of Treatments

Substance	INS018_055 30 mg[a,b]	INS018_055 60 mg[a,b,d]	Placebo 30 mg[e]
Pharmaceutical formulation	Hypromellose capsules	Hypromellose capsules	Hypromellose capsules
Unit strength	30 mg	30 mg (x2)	N/A
Posology	QD or BID[c]	QD	BID[f]
Mode of Administration	Oral	Oral	Oral
Source	InSilico Medicine	InSilico Medicine	InSilico Medicine

BID = twice a day; QD = every day

[a] INS018_055 will be supplied as solid, acetate salt drug substance with no excipients in hypromellose capsules containing 30 mg of INS018_055 per capsule (calculated as the free base form)

[b] Patients who enrolled into the study with baseline background SoC antifibrotic therapy (nintedanib, pirfenidone) will continue to take their own supply of respective therapy

[c] INS018_055 30 mg administered as QD or BID schedule will depend on the treatment arm into which the patient is assigned

[d] INS018_055 60 mg QD will be administered as 2 capsules of INS018_055 30 mg both taken together once daily

[e] Placebo matching in size, weight, color, and shape to INS018_055 30 mg and will not include the active compound

[f] Regardless of treatment arm, subjects will take 3 capsules (two in the morning and one in the evening) every day. Subjects assigned to INS018_055 30 mg QD treatment will take one INS018_055 30 mg + one placebo together in the morning; and one placebo in the evening. Subjects assigned to INS018_055 30 mg BID treatment will take one INS018_055 30 mg + one placebo together in the morning; and one INS018_055 30 mg in the evening. Subjects assigned to INS018_055 60 mg QD treatment will take two INS018_055 30 mg together in the morning; and one placebo in the evening. Subjects assigned to placebo treatment will take two placebo together in the morning; and one placebo in the evening.

4.1.2 Selection of Doses in the Study and Dose Modifications

The selection of doses was guided by two phase 1, randomized, double-blind, placebo-controlled, parallel-group, single ascending dose and multiple ascending dose studies of INS018_055 (NCT05154240) in healthy volunteers. Preliminary results show that

INS018_055 has a manageable side effect profile; the majority of TEAEs are mild and transient. The phase 1 studies are background, and final results are pending.

This proposed Phase IIa study will test 2 active doses of INS018_055 (30 mg and 60 mg) orally administered as 30 mg QD, 30 mg BID, or 60 mg QD for a period of 12 weeks. Nonclinical efficacy and safety studies have shown that pharmacological effects start at a 24-hour exposure level [area under the concentration-time curve (AUC_{0-24})] of approximately 300 h*ng/mL and reach a plateau at levels greater than 900 h*ng/mL. The no observed adverse effect level (NOAEL) exposures (AUC_{0-24}) in the 28-day toxicity studies in mice (3820 h*ng/mL for female, 4440 h*ng/mL for male) and dogs (2010 h*ng/mL for female, 2600 h*ng/mL for male) were clearly higher than the anticipated exposures associated with a pharmacologically active dose. The NOAEL exposure levels (AUC_{0-24}) in the 3-month toxicity in mice (4300 h*ng/mL for males and 5250 h*ng/mL for females) and dog (1000 h*ng/mL for males and 1030 h*ng/mL for females) were close to the exposure required for a maximum pharmacological effect. Thus, the therapeutic exposure levels (AUC_{0-24}) should be greater than 300 h*ng/mL and not markedly exceed 1000 h*ng/mL.

Based on these data and supported by physiologically based pharmacokinetic (PBPK) analysis (GastroPlus) of the available phase 1 data, the following dose levels and dosing schemes of INS018_055 have been selected for the planned phase IIa study: INS018_055 30 mg QD or 60 mg QD either as a single daily dose or in 2 divided doses alone or adjunct to SoC pirfenidone or nintedanib according to their respective labels. The doses of 30 mg QD and 60 mg QD in healthy volunteers after 7-day oral administrations led to exposure levels (AUC_{0-24} in plasma) of 438 and 1210 h*ng/mL on Day 7 when the steady state was reached, respectively (section 1.2.2). Thus, the selected doses are expected to be in the pharmacological range from half maximum efficacy to maximum efficacy and not anticipated to markedly exceed the NOAEL exposures in nonclinical species. Additionally, there was mean bound fraction (%) of 97.2% in human plasma and 93% in Beagle dog plasma, with about a 2-fold lower free fraction in human plasma. Therefore, from the free exposure perspective, 60 mg QD with the total exposure of 1210 h*ng/mL in humans will not exceed the free exposure at the dog NOAEL.

The dose of 60 mg/day will be given either as a single daily dose (60 mg QD) or in 2 divided doses per day (30 mg BID). This is based on the results of PBPK modeling of clinical plasma concentrations, which showed that the 60 mg QD dose will achieve plasma concentrations above the TNIK half maximal inhibitory concentration (IC_{50}) value for approximately 16

hours per day, while the BID dose may result in plasma concentrations above the TNIK IC_{50} value throughout the whole 24-hour period. By comparison of these 2 dosing schemes, it can be clarified whether a permanent inhibition of TNIK is required for maximum therapeutic efficacy.

In this phase IIa study, the exposure in patients with IPF at the doses of INS018_055 30 mg QD, INS018_055 30 mg BID, or INS018_055 60 mg QD (maximum 60 mg daily) is expected to fall within estimated therapeutic range and below the human systemic exposure limit of INS018_055 based on animal toxicology studies. In addition, based on the current knowledge on pharmacodynamics of INS018_055, nintedanib, and pirfenidone, we do not anticipate DDIs among these treatments.

4.1.3 Method of Assigning Patients to Treatment Arms

After the investigator and/or study staff confirm that a subject has met all eligibility criteria (meet all inclusion criteria and none of the exclusion criteria), each eligible subject will be randomized to a treatment group according to a 1:1:1:1 ratio randomization plan. Randomization will occur at Visit 2 via Interactive Response Technology (IRT). The treatment arms are:

- INS018_055 30 mg QD
- INS018_055 30 mg BID
- INS018_055 60 mg QD
- Placebo

4.1.4 Drug Assignment and Administration of Doses for Each Patient

The 12-week treatment period begins and ends with Visit 2 and Visit 6, respectively. Subjects being treated with background SoC antifibrotic therapy (nintedanib, pirfenidone) at the time of randomization will maintain their therapy throughout the study. Subjects will orally self-administer their assigned treatment for 12 weeks [until Visit 6 (EOT)].

- Subjects will be given medicine kits at each visit starting with Day 1 (Visit 2). INS018_055 will be supplied as solid, acetate salt drug substance, no excipients, in hypromellose capsules, 30 mg of INS018_055 per capsule (calculated as the free base form).

- Subjects will be instructed to maintain a consistent treatment schedule for taking their assigned treatments. Regardless of treatment arm, subjects will take 3 capsules (two in the morning and one in the evening) every day:
  - INS018_055 30 mg QD treatment arm: one INS018_055 capsule + one placebo together in the morning; and one placebo in the evening. Subjects should take their treatment at the same time every day +/- 30 min with interval of 12 hours between doses (+/- 1 hour) and maintain the same schedule for their other medications
  - INS018_055 30 mg BID treatment arm: one INS018_055 30 mg + one placebo together in the morning; and one INS018_055 30 mg in the evening. Subjects should take their treatment at the same time every day +/- 30 min with interval of 12 hours between doses (+/- 1 hour) and maintain the same schedule for their other medications
  - INS018_055 60 mg QD treatment arm: two INS018_055 together in the morning and one placebo in the evening. Subjects should take their treatment at the same time every day +/- 30 min with interval of 12 hours between doses (+/- 1 hour) and maintain the same schedule for their other medications.
  - Placebo arm: two placebo together in the morning and one placebo in the evening. Subjects should take their treatment at the same time every day +/- 30 min with interval of 12 hours (+/- 1 hour) between doses and maintain the same schedule for their other medications.

Table 5. Dosage and Treatment Schedule

Regardless of treatment arm, subjects will take 3 capsules (two in the morning and one in the evening) every day

Treatment[a]	INS018_055 30 mg daily		INS018_055 30 mg twice daily		INS018_055 60 mg daily		Placebo	
Time of day[b]	AM	PM	AM	PM	AM	PM	AM	PM
API 30 mg (number of capsules)	1	0	1	1	2	0	0	0
Placebo (number of capsules)	1	1	1	0	0	1	2	1

API = active product ingredient; BID = twice a day; QD = daily

[a] Subjects will be instructed to maintain a consistent treatment schedule and take their assigned treatments. Subjects with background SoC antifibrotic therapy (nintedanib, pirfenidone) at the time of randomization will maintain their therapy throughout the study.

[b] AM refers to 06:00 and 11:00 in the morning. PM refers to18:00 and 23:00 in the evening.

Subjects should make every effort to take their treatment every day between 06:00 and 11:00 in the morning and between 18:00 and 23:00 in the evening. INS018_055 should be taken with a glass of water (~250 mL). Subjects will be instructed to return used bottles at every visit. Sites will train subjects about the treatment schedule and follow up between visits.

If a subject forgets to take a dose of INS018_055, the patient can skip the dose if the time window to the next dose is < 8 hours. The next dose should be taken as scheduled.

4.1.5 Blinding and Procedures for Unblinding

4.1.5.1 Blinding

Subjects, investigators, site study staff, reviewers, and everyone involved in study conduct or analysis, with the exception of bioanalytics and possibly DSMB members, or with any other interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after database lock.

Access to the randomization code will be kept restricted until its release for analysis.

The randomization codes will be provided to bioanalytics to allow identification of samples from subjects assigned to placebo treatment. Bioanalytics will not disclose the randomization code, including which subjects have been tested or the results of their measurements, until the trial is officially unblinded.

4.1.5.2 Unblinding and Breaking the Code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the study drug must be revealed in order to provide appropriate medical treatment or otherwise assure the safety of study participants. Investigators are encouraged to discuss the need for unblinding with the medical monitor as warranted before unblinding the subject. The reason for unblinding must be documented in the source documents and/or appropriate case report form (CRF).

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for InSilico Medicine to access the randomization code for individual subjects during the course of the study. Access to the code will only be given to authorized InSilico Medicine Pharmacovigilance (PV) team members for processing in the PV database system and not be shared further.

4.1.6 Packaging, Labeling, and Re-supply of the Study Treatment

The study treatment INS018_055 will be provided by InSilico Medicine or a designated CRO. The INS018_055 capsules will be packaged in high-density polyethylene bottles sealed with polypropylene continuous-thread child-resistant caps with an induction sealed and aluminum-faced liner. Each bottle is filled with 30 capsules.

INS018_055 will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites. For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage Conditions

Study treatments, including INS018_055 and placebo, will be kept in their original packaging in a secure limited access storage area according to the recommended storage conditions on the provided medication label. A temperature log must be maintained for documentation. The products will be stored at 15-25 ˚C. If the storage conditions are found to be outside the specified range, the investigator should contact InSilico Medicine immediately.

4.1.8 Drug Accountability

The investigator or designee will receive the investigational drugs delivered by InSilico Medicine (or designated CRO) when the following requirements are fulfilled:

- Approval of the clinical study protocol by local IRB / ethics committee, HA/RA approval
- Availability of a signed and dated clinical study contract between InSilico Medicine and the investigational site
- Approval/notification of the regulatory authority, e.g., competent authority
- Availability of the curriculum vitae of the Site Principal Investigator
- Availability of a signed and dated clinical study protocol
- Availability of the proof of a medical license for the Site Principal Investigator
- Availability of signed and dated FDA Form 1572 (if applicable)

Investigational drugs are not allowed to be used outside the context of this study protocol. Investigational drugs must not be forwarded to other investigators, clinicians, or clinics internal or external to the study site. Subjects should be instructed to return unused investigational drug directly to site study staff.

The investigator or designee must maintain records of the delivery of study treatments, including INS018_055 and placebo, to the study site, current inventory at the site, use by each subject, and return of products to InSilico Medicine (or designated CRO) or warehouse / drug distribution center. The investigator should contact InSilico Medicine about questions related to disposal of unused products. InSilico Medicine (or designated CRO) or warehouse / drug distribution center will maintain records of the disposal.

Documentation of study treatments will include dates, quantities, batch/serial numbers, expiry (‘use-by’) dates, and the unique code numbers assigned to the investigational medicinal product and study subjects. The investigator or designee will maintain records that adequately document that the subjects were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to InSilico Medicine (or designated CRO), the investigator or designee must verify that all unused or partially used study treatments have been returned by the clinical study subject and that no remaining study treatments are in the investigator’s possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, AND RESTRICTIONS

4.2.1 Other Treatments and Emergency Procedures

There are no special emergency procedures to be followed. A temporary treatment interruption for up to one week is allowed to manage adverse events, such as GI events, need to take restricted medication etc. This will be documented on the respective eCRF page. A maximum total duration of interruptions of 2 weeks is allowed.

4.2.2 Restrictions

4.2.2.1 Restrictions Regarding Concomitant Treatment

All concomitant or rescue therapies will be recorded on the appropriate eCRF page.

Marketed antifibrotic treatment (nintedanib or pirfenidone) is allowed at study enrollment. Per the study inclusion criteria (section 3.3.2), subjects already taking pirfenidone or nintedanib may be enrolled if their regimen has been stable for ≥ 8 weeks prior to Visit 1. Table 6 shows the restricted medications during the study. Lists of potent inhibitors and inducers of CYP3A and CYP1A2 can be found in section 10.8.

Table 6. Restricted Medications During the Study

Medication Evaluation at Visit 1	Prior to Study Enrollment	Screening Period	Treatment Period	Follow up Period
Nintedanib or pirfenidone if stable regimen[a]	Allowed	Allowed	Allowed	Allowed
Nintedanib or pirfenidone for patients not already on SoC antifibrotic therapy[b]	Not allowed	Not allowed	Not allowed	Not allowed
Nintedanib or pirfenidone for patients who are not taking these therapies[b]	Not allowed	Not allowed	Not allowed	Not allowed

Oral corticosteroids at daily dose >15 mg prednisone or equivalent[c]	Not allowed	Not allowed	Not allowed[d]	Allowed
Combination of prednisone, azathioprine, and N-acetylcysteine, ambrisentan, or imatinib[e]	Not allowed	Not allowed	Not allowed	Not allowed
Controller therapies for patients with COPD[f]	Allowed	Allowed	Allowed	Allowed
Moderate/strong CYP3A4 inhibitors/inducers [h]	Allowed	Not allowed	Not allowed	Allowed
Moderate/strong CYP1A2 inhibitors/inducers[g,h]	Allowed	Not allowed	Not allowed	Allowed

[a] Only allowed for subjects with baseline background SoC pirfenidone or nintedanib as monotherapy that has been stable ≥ 8 weeks prior to Visit 1. Subjects will continue to take their own supply of respective therapy throughout the study. In no other circumstances will subjects be allowed to take pirfenidone or nintedanib. Section 3.3.2 lists the study inclusion criteria.
[b] Subjects who enroll into the study and are not currently taking SoC pirfenidone or nintedanib or subjects who have never been treated with pirfenidone or nintedanib will not be allowed to take pirfenidone or nintedanib during the study. Section 3.3.2 lists the study inclusion criteria
[c] Oral corticosteroids at daily dose of >15 mg prednisone or equivalent is not allowed during the 30 days prior to randomization (Visit 2). A table of equivalent doses of corticosteroids can be found in section 10.7
[d] Prednisone >15 mg/day or equivalent can be prescribed during the treatment period in case of acute exacerbation as described in section 5.6.1.3. A table of equivalent doses of corticosteroids can be found in section 10.7
[e] Combination of prednisone, azathioprine, and N-acetylcysteine, ambrisentan, or imatinib within 30 days prior to Visit 2 is not allowed. Section 3.3.3 lists the study exclusion criteria
[f] Controller therapies for subjects with comorbid COPD are allowed if subjects are receiving ≤ 2 controller therapies (2 different mechanisms of action) and there have been no changes to their controller regimen within 3 months prior to Day 1. Section 3.3.3 lists the study exclusion criteria
[g] Applies to subjects who are taking SoC pirfenidone
[h] Also include Chinese herbal medicine that have DDI potentials.

4.2.2.2 Restrictions on Diet and Lifestyle

All inhaled products, including cigarettes, pipes, cigars, e-cigarettes/ vaping, and marijuana, are prohibited throughout the study.

Subjects should refrain from consuming grapefruit or grapefruit juice, pomelo, Seville orange or Seville orange-containing products juice or St. John's Wort during the entire study. These are considered likely to interfere with safe conduct of the study.

Patients should refrain from consuming methylxanthine-containing drinks or foods (such as coffee, tea, cola, energy drinks, and chocolate) in the 24 h preceding each on site visit.

4.2.2.3 Contraception Requirements

Subjects must agree to use acceptable contraceptive methods during the study to avoid pregnancy, from first dosing day (Visit 2, Day 1) until 3 months after study completion (Visit 7, EOS). This applies to female subjects of childbearing potential and male subjects with partners of childbearing potential. Acceptable methods of contraception include: barrier contraception and a medically accepted contraceptive method for the female partner (intra-uterine device with spermicide, hormonal contraceptive used for $\geq$ 2 months prior); true sexual abstinence (when this is in line with the preferred and usual lifestyle of the subject); or surgically sterilized, including vasectomy for men.

4.3 TREATMENT COMPLIANCE

Subjects will be asked to bring remaining study medication, including INS018_055 and placebo, as well as empty package material with them to the study visits. Based on capsule counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorized by the sponsor.

$$\text{Treatment Compliance (\%)} = \frac{\text{Number of capsules actually taken}}{\text{Number of capsules which should have been taken as directed by the investigator}} \times 100$$

5 ASSESSMENTS

5.1 OVERVIEW OF PROCEDURES AT STUDY VISITS

The following sequence of procedures at each visit (where applicable) is recommended:

Table 7. Order of Procedures During Study Visit

Timing at Study Visit	Procedures
Start of visit	• PRO(LCQ) • Vital Signs, body weight, Physical Examination • Evaluation AE, concomitant medications
Procedures	• ECG • Spirometry • DLCO • Laboratory testing, including blood sampling including pre-dose PK, Biomarker and proteome in serum/plasma • 6MWD after 30 mins of rest, Borg CR10
End of visit	• Review of PRO (LCQ) for completeness • Return of study medication bottles • IRT call • Schedule next visit if applicable

5.2. SAFETY LABORATORY PARAMETERS

Safety laboratory parameters to be assessed are listed in Table 8 according to the Schedule of Study Activities and will be performed by site laboratory. The respective reference ranges will be provided in the ISF. Erythrocyte sedimentation rate (ESR) will be performed on-site. The value for ESR will be reported directly by the site in the eCRF. Liver function tests and lipid panel will be drawn at each study visit.

Subjects will fast for the blood sampling.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF. It is the responsibility of the investigator

to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (5.6).

In the case that the criteria for hepatic injury are fulfilled, a number of additional measures will be performed. Please refer to 5.6 provided in the EDC system. The amount of blood taken from the affected subject will be increased due to this additional sampling.

Table 8 lists the safety laboratory tests. eGFR will be analyzed and calculated at the same timepoints as other safety laboratory parameters (Schedule of Study Activities). eGFR will be calculated by using the CKD-EPI formula (10.6) and using the Jaffe assay for serum creatinine measurement, IDMS standardized.

Table 8. Safety Laboratory Tests

Functional Lab Group	Name of Test
Hematology	Hematocrit, Hemoglobin, RBC count, reticulocyte count, WBC with differential (automatic WBC differential includes the relative and absolute quantification of neutrophils, eosinophils, basophils, monocytes and lymphocytes. If automatic WBC differential is abnormal, manual WBC differential is advised to include polymorphonuclear neutrophils (segs), band neutrophils (stabs), eosinophils, basophils, monocytes and lymphocytes), platelet count, erythrocyte sedimentation rate (ESR).
Automatic WBC Differential (relative and absolute)	Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Polymorphnuclear neutrophils (segs), Band neutrophils (stabs), Eosinophils, Basophils, Monocytes, Lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT), Prothrombin time (Quick's test and INR), Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT), Alanine transaminase (ALT/GPT), Alkaline

	phosphatase (AP), Gamma-glutamyl transferase (GGT), Creatine kinase (CK), CK-MB only if CK is elevated
Hormones	Thyroid stimulating hormone (TSH), fT3, fT4
Substrates	Plasma glucose, Creatinine, Total bilirubin, Direct and indirect bilirubin, Total protein, High sensitivity C-Reactive Protein (hs CRP), blood urea nitrogen (BUN) or urea, Uric acid, Total cholesterol, Triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), Albumin
Electrolytes	Sodium, Potassium, Chloride, Calcium, Inorganic phosphate
Urine analysis	Qualitative/semi-quantitative, appearance, color, pH, specific gravity, glucose, erythrocytes, leukocytes, protein, urobilinogen, urine bilirubin.

Guidance on transaminase values and treatment management are shown below. Site investigators should follow Table 9, and refer to the package insert for nintedanib and pirfenidone where relevant. LFT assessments should be performed prior to starting treatment for INS018_055, nintedanib, and pirfenidone. Adjustments to treatment should be made according to the AST and ALT laboratory values as outlined below.

Table 9. Guidance on Transaminase Laboratory Values and Treatment Management

Criteria	**INS018_055**	**Nintedanib or Pirfenidone**
LFT assessment schedule	• Conduct LFT prior to start of treatment	• Conduct LFT prior to start of treatment • Follow package insert
AST/ALT < 3x ULN	• Continue treatment	• Follow package insert
AST/ALT > 3x ULN – 5x ULN without liver damage	• Interrupt treatment until return to 1.5x ULN and normal bilirubin	• Follow package insert

AST/ALT > 3x ULN – 5x ULN with signs of liver damage	• Discontinue treatment	• Follow package insert
AST/ALT > 5x ULN	• Discontinue treatment • Perform hepatic serologies, ultrasound of the liver, and other tests per investigator discretion	• Follow package insert

5.3 PATIENT-REPORTED OUTCOMES

Subjects should complete the patient reported outcome questionnaire on his/her own as defined in the Schedule of Study Activities. Ideally, the subject should complete the questionnaire in a quiet area/room prior to any other study-related examination. Study site personnel will check the questionnaires for completeness prior to the subject leaving the site, but the response to each item should not be scrutinized. In instances where a patient cannot give or decide upon a response, no response should be recorded. The scores will be transcribed into the eCRF by designated site personnel.

5.3.1 Leicester Cough Questionnaire

The LCQ (section 10.1) will be self-administered by the subject at study visits according to the Schedule of Study Activities. The LCQ is a 19-item questionnaire that assesses cough related QoL (Birring 2003). It examines 3 domains: physical, psychological and social. The questionnaire was revised so that each item related to the patient's experience within a 24-hour time frame. The range for the total score on the LCQ is 3-21, and each domain score ranges from 1-7. The overall score for the LCQ for each patient is calculated by adding the individual domain scores. A higher score indicates a better QoL.

5.4 PHYSICAL EXAMINATION

A complete physical examination will be performed at the time points specified in the Schedule of Study Activities. Physical examination includes, at a minimum, assessment of a subject's general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. All abnormal findings at baseline will be recorded on the Baseline Condition eCRF page. New abnormal findings or worsening of baseline conditions detected at subsequent

physical examinations, if judged clinically relevant, will be recorded as adverse events on the appropriate eCRF page.

Measurement of height will be performed at the screening visit only.

Body weight will also be evaluated at each visit. Body weight should be measured with the patient wearing indoor clothing and without shoes. For each subject, weight should be measured consistently in the morning at all visits after emptying the bladder. The results must be included in the source documents available at the site.

5.5 VITAL SIGNS

Vital signs will be evaluated at the time points specified in the Schedule of Study Activities and prior to blood sampling. This includes body temperature, systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute). Subjects should be in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

5.6 ADVERSE EVENTS

Safety will be assessed through the collection and evaluation of AEs, including TEAEs, SAEs and AESIs. Safety will also be assessed based on physical examinations, vital sign measurements, clinical laboratory assessments and ECGs. Common Terminology Criteria for AEs (CTCAE) v5.0 grading scale will be used for grading of AEs. A DSMB will oversee the safety of the study and will have scheduled meetings.

5.6.1 Definitions of Adverse Event

5.6.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to 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 product, whether or not considered related to the medicinal product. The following should also be recorded as an AE in the EDC:

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the EDC.

5.6.1.2 Serious Adverse Event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria listed below. All SAEs should be recorded in the EDC.

- Results in death
- Life-threatening, defined as an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Congenital anomaly / birth defect
- Deemed serious for any other reason if it is an important medical event based on appropriate medical judgement which may jeopardize the subject and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, convulsions that do not result in hospitalization, or development of dependency or abuse

5.6.1.3 Acute IPF Exacerbation

The most recent definition of acute IPF exacerbation will be used. [Collard 2016] The AEs will not be adjudicated. Acute IPF exacerbation will be defined as an acute, clinically significant, respiratory deterioration characterized by evidence of new widespread alveolar abnormality with all of the following:

- Acute worsening or development of dyspnea typically of < 1 month duration

- Computed tomography scan with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with IPF
- Deterioration not fully explained by cardiac failure or fluid overload.

Events that are clinically considered to meet the definition of acute IPF exacerbation but fail to meet diagnostic criteria due to missing CT data must be reported as "suspected acute exacerbations of disease under investigation" (as long as this assessment persists).

5.6.1.4 AEs of Special Interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g., the potential for AEs based on knowledge from other compounds in the same class.

The following are considered 'potential' AESIs:

Gastrointestinal: diarrhea, nausea, vomiting, clinical bleeding

Hepatic injury. A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥ 3-fold ULN combined with an elevation of total bilirubin ≥ 2-fold ULN measured in the same blood draw sample, or
- Aminotransferase (ALT, and/or AST) elevations ≥ 10-fold ULN

These lab findings constitute a hepatic injury alert. Subjects with these lab abnormalities need to be followed up. In case of clinical symptoms of hepatic injury, i.e., icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc., without available laboratory results (ALT, AST, total bilirubin), the investigator should make sure these parameters are analyzed. If necessary, these parameters can be analyzed in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the investigator should contact the medical monitor.

5.6.2 Intensity (severity) of Adverse Events

The intensity (severity) of the AE should be judged based on the CTCAE v5.0.

5.6.3 Causal Relationship of Adverse Events

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between an AE and the given study treatment. All relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history should be considered.
Site investigator should assess the AE based on 5 scales for the causality/ relatedness:

- Definite: The AE is clearly related to the investigational drug or study treatment
- Probable: The AE is likely related to the investigational drug or study treatment
- Possible: The AE may be related to the investigational drug or study treatment
- Unlikely: The AE is doubtfully related to the investigational drug or study treatment
- Unrelated: The AE is clearly NOT related to the investigational drug or study treatment

5.6.4 Collecting and Reporting of Adverse Events

5.6.4.1 Collection of AEs

The investigator shall maintain and keep detailed records of all AEs in the study subject files. The following must be collected and documented in the eCRF by the investigator:

- From the signing of the informed consent until a study subject's end of study visit, all AEs (serious and non-serious) and all AESIs must be collected and documented in the eCRF. All non-serious ongoing AEs that occurred prior to the time of first dose will be captured as medical history.
- After a study subject's EOS visit, the investigator does not need to actively monitor the patient for new AEs. However, the investigator should report any study treatment-related SAEs and study treatment-related AESIs of which the investigator may become aware of by any means of communication, e.g., phone call. These AEs should be reported in the eCRF.

5.6.4.2 Reporting AEs to the Sponsor and Timelines

The investigator must report SAEs on the SAE form within 24 hours to the InSilico Medicine's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the InSilico Medicine upfront via telephone and or via email. This does not replace the requirement to complete the SAE report (in the EDC).

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after a subject's EOS must be followed until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.6.4.3 Pregnancy

In rare cases, pregnancy might occur in a clinical study. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study subject within 24 hours. This can be done by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male study subject becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed and reported to the InSilico Medicine's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B). If there is an SAE and/or AESI associated with the pregnancy an SAE and/or AESI form must be completed in addition.

5.7 ELECTROCARDIOGRAM RECORDING

5.7.1 ECG Procedure

In order to achieve a stable heart rate (HR) at rest and to assure high-quality recordings at comparable resting phases, all ECGs will be recorded for 10-sec duration after the subjects have rested for ≥ 10 min in a supine position. Study site staff will be instructed to assure for the subject a relaxed and quiet environment to optimize complete rest conditions during the recordings. Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerized electrocardiograph, at the time points given in the Schedule of Study Activities. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven or limb leads modified by Mason and Likar (hips and shoulders instead of ankles and wrists). For patient eligibility at screening, if the ECG parameters are not met at first take, the ECG should be repeated 2 more times, in which case the average of the 3 QTcF (or QRS interval) values should be used to determine the subject's eligibility. Additional (unscheduled) ECGs may be recorded for safety reasons.

5.7.2 ECG Evaluation

This will include the determination of cardiac QRS-axis as assessed by the ECG machine's algorithm as well as the intervals RR, PR, QRS and QT measured semi- automatically. Heart rate (HR) and the QT interval corrected for HR (QTcF) will be determined by the site equipment. All ECGs will be evaluated by the investigator or a designee. For the inclusion (section 3.3.2) or exclusion (section 3.3.3) of a subject and for the assessment of cardiac safety during the study, the QT and QTcF values generated by the ECG machines will be used. If the ECG machines cannot provide QTcF values directly, QTcF can be calculated using the Fridericia (QTcF) formula: $QTcF = QT/RR^{1/3}$, where RR represents RR interval and RR=60/HR.

5.8 SPIROMETRY

FVC and FEV1 will be assessed using standardised spirometry equipment which will be provided centrally with supplies of pre-calibrated disposable flow sensors.These sensors demonstrate variability within the required standards of +/-3% determined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2019 guidelines. [Graham 2019]. The single use Pneumotach (PT) including a mouthpiece that is pre-calibrated as part of the manufacturing process and is tested within the range of +/-1.5% of the expected value.

Efforts should be made to schedule spirometric measurements at approximately the same time of the day at each visit ± 90 min. Baseline measurement (Visit 2) will be the reference visit. On days of study visits, subjects must refrain from strenuous activity at least 12 hours prior to pulmonary function testing. Subjects should also avoid cold temperatures, environmental smoke, dust, or areas with strong odors, e.g., perfumes. If treated with bronchodilators, the wash-out period for short-acting bronchodilators, long-acting twice-daily bronchodilators, and long-acting once-daily bronchodilators is 4 hours, 12 hours, and 24 hours, respectively. Subjects should be instructed to do their best to adhere to this.

Spirometry will be conducted while the patient is in a seated position. It is preferable that the same trained individual performs the PFTs for a given subject. The best of three efforts will be defined as the highest FEV1 and the highest FVC each obtained on any of three blows meeting the 2019 ATS/ERS guideline criteria (maximum of eight attempts) [Graham 2019]. Spirometry results captured by spirometers provided by the sponsor will be electronically transmitted and confirmed by central reading. Only data from acceptable spirometry maneuvers will be used for eligibility confirmation and data analysis. For baseline and EOT visits, if multiple acceptable spirometry results are reported for one visit, mean values of the acceptable results will be used for data analysis. For detailed information, refer to the statistical analysis plan

For each subject, spirometry testing and DLCO should always start at approximately the same time of day. DLCO should always be performed after spirometry after subjects are well-rested.

5.9 DLCO

Each study site will use its own equipment to assess carbon monoxide diffusion capacity during the single breath diffusion test and conduct all measurements using with the same equipment. Single breath diffusion test will be carried out according to the ATS/ERS guidelines. [Graham 2017] Before the test, site staff should thoroughly demonstrate the maneuvers and be certain that subject understands the instructions. The mean value between $\geq$ 2 acceptable tests should be reported. Sites will enter the absolute DLCO results using data from their own equipment software. The predicted DLCO, % predicted DLCO, and corrected % predicted DLCO will be calculated by statistician programmer using the GLI equation. Please refer to section 10.2 for additional information.

Only data from acceptable DLCO maneuvers will be used for eligibility confirmation. No more than three DLCO sessions should be performed during the screening period. Baseline measurement (Visit 2) will be the reference visit.

5.10 6MWD

Subjects should rest for 30 minutes prior to performing the 6-minute walk test. Instruct the subject to walk on a flat, hard surface. Time the walk for 6 minutes. After 6 minutes have passed, measure the distance the patient has walked. [Solway 2001] For subjects who require supplemental oxygen to maintain their ADL (SpO2<88% at resting state), up to a maximum of oxygen 6 L/min is allowed so that patients should maintain SpO2 ≧ 83%. [du Bois 2011] [ATS 2002] [Lama 2003] [Hu 2022]

Before and after the 6MWD, subjects will complete the Borg scale. Subjects will grade their level of dyspnea on a scale of 0 (no dyspnea) to 10 (maximal dyspnea) before walking. After walking, subjects will be reminded of the level they selected pre-walk and then asked to grade again their level of dyspnea. [Borg 1982] [ATS 2002]

5.11 DRUG CONCENTRATION OF MEASUREMENTS AND PHARMACOKINETICS

5.11.1 Assessment of Pharmacokinetics

Blood samples for plasma concentrations of INS018_055 and metabolites (INS018_063 and INS018_095) will be collected at specific time points:

- Visit 2: pre-dose and post-dose
- Visits 3, 4 and 5: pre-dose
- Visit 6 (EOT): pre-dose and post-dose

Blood samples for serum or plasma concentrations of biomarkers will also be collected:

- Visit 2: pre-dose
- Visits 3, 4 and 5: pre-dose
- Visit 6 (EOT): pre-dose

See section 10.4 for further details. Date and clock time of drug administration and PK sampling will be recorded in the CRFs. The actual sampling will be used for determination of PK parameters.

5.11.2 Monitoring of Concentrations of Background SoC Therapy

Blood samples for plasma concentrations of pirfenidone and nintedanib will be collected at the following time points (section 10.4)

- Visit 2: pre-dose (i.e., prior to pirfenidone or nintedanib and INS018_055 dosing, in order to get the baseline trough plasma concentration of pirfenidone or nintedanib)
- Visits 3, 4, 5, and 6: pre-dose

5.11.3 Methods of Sample Collection

During the treatment period, at Visits 2 through 6 subjects will receive a study diary to precisely record the time of drug intake for the days preceding the next visit.

For quantification of drug plasma concentrations of INS018_055, venous blood will be collected using a pre-labeled ethylenediaminetetraacetic acid (EDTA) containing blood drawing tube at the times indicated in the and section 10.4. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. A detailed description of sample collection and handling is provided in the Lab Manual in the ISF.

After completion of the trial the plasma samples may be used for further methodological investigations, e.g., for stability testing, assessment of metabolites. However, only data related to the analyte and/or its metabolite(s) including anti-drug antibodies (if applicable) will be generated by these additional investigations. The study samples will be discarded

after completion of the additional investigations but not later than 5 years after the final study report has been signed.

5.11.4 Analytical Determinations

5.11.4.1 Analytical Determination of Plasma Concentrations

All samples from patients on active study treatment will be analyzed. For subjects on placebo, only one time point (one hour post-dose) will be analyzed in order to demonstrate absence of drug. If there is a quantifiable drug concentration in question, then all PK samples from the subject on placebo would be analyzed.

INS018_055 concentrations in plasma will be determined by a validated high performance liquid chromatography with tandem mass spectrometry (HPLC-MS/MS) assay. The analysis will be performed under the responsibility of InSilico Medicine.

As described in section 4.1.5 the bioanalyst will be unblinded during sample analysis.

5.12 ASSESSMENT OF BIOMARKER(S)

Serum samples will be used for explorative endpoint assessment. A part of the serum will be used for the detection of biomarkers associated with IPF pathology. These include levels of MMP-7, MMP-2, MMP-9, TGF-beta, IL-6, TIMP-1, IL-1beta in blood samples. In addition, part of serum sample will be used to perform high-throughput proteomic analysis on blood proteome to further explore the mechanism of action of INS018_055 in patients with written informed consent obtained. Remaining samples will be stored for a maximum of 3 years after approval of the clinical trial report.

Correct, complete, and legible documentation of drug administration and blood sampling times is mandatory to obtain data of adequate quality for biomarker analysis. A detailed overview of biomarker sample collection visits and time points are outlined in the Schedule of Study Activities and respective footnotes. High-throughput proteomic analysis will be managed through a sponsor designated laboratory. Details about sample collection and sample handling will be provided in the lab manual.

5.12.1 Blood Biomarkers

Effects of INS018_055 treatment on several protein biomarkers, including MMP-7, MMP-2, MMP-9, TGF-β, IL-6, TIMP-1, IL-1β as well as the mechanism of action of INS018_055 in blood proteome will be evaluated.

5.12.2 Methods of Sample Collection

Whole blood will be collected for the preparation of serum or plasma. Collection time points are outlined in the Schedule of Study Activities. Correct, complete and legible documentation of drug administration and blood sampling times is mandatory to obtain data of adequate quality for biomarker analysis. A detailed description of biomarker sample collection and sample handling is provided in the ISF.

5.12.3 Analytical Determinations

All biomarkers assessed in this trial are considered exploratory and qualified assays will be used according to the sponsor's procedures. Characteristics of the analytical methods for the analysis of plasma or serum biomarkers will be given in detail in the analytical report.

Changes in serum or plasma biomarkers will be analyzed over time pre and post treatment with INS018_055. All assessed biomarkers will either be analyzed at the sponsor or at a CRO. The results of biomarker analyses may be included into the clinical trial report, or reported separately. Refer to laboratory manual.

5.12.4 Appropriateness of Measurements

All measurements conducted for primary and secondary endpoints are using standard methods. Refer to section 3.2 for the discussion of the choice of FVC as primary endpoint. The pharmacokinetic parameters and measurements outlined in section 5.11 generally used as measurements to assess drug exposure. Measures conducted for exploratory endpoints might be new methodologies already used in clinical trials but not yet validated for IPF.

6 INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

This phase IIa study will follow the measurements and assessments scheduled to occur 'before' study medication administration on Day 1 (Schedule of Study Activities). The aim is to complete these procedures within a 2 h-period prior to study drug administration (including pre-dose values for PK and biomarkers). For planned individual plasma concentration sampling times refer to the section 10.4. These nominal times should be adhered to as closely as possible, and the actual sampling times will be recorded and used for determination of PK parameters.

If a patient misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

For the details of the modifications refer to section 6.2.

6.2 SCREENING PERIOD

After having been informed about the trial, subjects will be required to give written informed consent in accordance with ICH-GCP and local legislation prior to study enrollment. After informed consent is obtained (signed and dated), study eligibility criteria (inclusion and exclusion) should be checked according to Schedule of Study Activities.

For information regarding laboratory tests, ECG, vital signs, body weight and physical examination, refer to section 5.2 and section 5.4, respectively. For information on spirometry (FEV1 and FVC) and DLCO refer to section 5.8 and section 5.9, respectively.

An historical HRCT scan can be used to determine eligibility, provided that the scan was performed within the past 12 months prior to Visit 1. If the historical scan is not available or an available scan fails to meet the required image acquisition specifications, an HRCT may be performed after consent to determine eligibility. Central review of all HRCT scans will be performed to confirm diagnosis of IPF, prior to randomization. Confirmation of diagnosis must be available prior to Visit 2. HRCT should not be repeated for eligibility if previous scan was taken within the past 3 months. To perform an HRCT within the trial, all local regulatory requirements to perform an HRCT have to be met. If required, the HRCT scan

should be performed as close to screening date as possible, preferably once eligibility is confirmed based on other parameters, to avoid unnecessary scans for patients who are found ineligible based on other criteria.

Screening period may be extended up to 14 days for administrative reasons. Approval should be obtained from the sponsor who will also determine if any tests specified in the protocol must be repeated before the randomization visit (Visit 2).

6.3 TREATMENT PERIOD

Subjects who meet all inclusion criteria and none of the exclusion criteria, including positive HRCT review, will be randomized at Visit 2 in a 1:1:1:1 ratio to 1 of 4 treatment arms:

- INS018_055 30 mg QD
- INS018_055 30 mg BID
- INS018_055 60 mg QD
- Placebo

Subjects already taking SoC antifibrotic therapy (pirfenidone or nintedanib) at study enrollment should maintain their therapy at a stable dose as much as possible during the study. Subjects already taking pirfenidone or nintedanib will continue to use their own supply.

Subjects who are not taking pirfenidone or nintedanib at Visit 1 are not allowed to start these therapies while enrolled in the study. Subjects who have never been treated with pirfenidone or nintedanib are not allowed to start these therapies while enrolled in the study.

At the beginning of each study visit during treatment phase, investigator and site personnel should check the well-being of the subject as well as prepare all requirements for conduct of the visit. Patients will complete the LCQ PRO described in section 5.3.1.

Safety laboratory tests will be performed as described in section 5.2.

FVC has to be measured at the same time ± 90 min (use Visit 1 as reference time). DLCO should be done after FVC measurements. Patients should rest between FVC and DLCO.

Subjects will self-administer INS018_055 30 mg QD, 30 mg BID, 60 mg QD, or placebo from Day 1 onwards according to their assigned treatment arm. All study medication will be taken orally. The patient will bring back all study medication, used and unused, at each at each study visit.

Pre-dose PK samples will be collected at Visits 2 through 6. At Visits 2 and 6 post-dose samples will also be taken. Samples will be obtained at time points shown below. Refer to section 10.4 for additional details.

- Week 0 (Day 1)
  - Pre-dose: within 45 minutes prior to morning dosing
  - Post-dose (after morning dosing): 0.25 (± 5 min), 0.5 (± 5 min), 1 (± 5 min), 2 (± 5 min), 4 (± 5 min), 6 (± 10 min), and 24 hours (± 30 min) (prior to Day 2 dosing)
- Weeks 2, 4, and 8
  - Pre-dose: within 45 minutes prior to morning dosing
- Week 12
  - Pre-dose: within 45 minutes prior to morning dosing
  - Post-dose (after morning dosing): and 0.25 (± 5 min), 0.5 (± 5 min), 1 (± 5 min), 2 (± 5 min), 4 (± 5 min), 6 (± 10 min), 24 (± 30 min), and 48 hours (± 60 min)

Blood samples for serum or plasma concentrations of biomarkers will be collected pre-dose at Visits 2 through 6.

At Visits 2 through 5, subjects will receive a study diary and will be instructed to record precisely the day and time that they take study treatment (INS018_055, placebo). Subjects will bring the study diary to the next study visit. Visit 6 will be the End of Treatment visit. A follow up EOS visit (Visit 7) will take place ~1 week after Visit 6.

6.4 FOLLOW UP PERIOD AND STUDY COMPLETION

A follow up period of a minimum of 7 days (+3 days) will be required. All patients will complete an end of trial visit (Visit 7). For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the end of trial period, see section 5. All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically

acceptable level is achieved. All (S)AEs persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").

7 STATISTICAL ANALYSIS PLAN

The primary objective is to evaluate the safety and tolerability of INS018_055 orally administered for up to 12 weeks in adult subjects with IPF compared to placebo. This study also aims to demonstrate proof of concept of efficacy of INS018_055 on lung function.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No hypothesis testing will be performed in the confirmatory sense. All the analyses will be performed in an exploratory fashion to better understand the efficacy and safety profile of INS018_055 in patients with IPF.

7.2 PLANNED ANALYSES

7.2.1 General Considerations

The following subject populations are defined:

Safety Population: The safety population will include all subjects who receive at least 1 dose of study treatment.

ITT Population: The intent-to-treat (ITT) population will include any randomized subjects.

PK Population: The PK population will include subjects who receive at least1 dose of study treatment and have a majority of scheduled PK samples drawn that allow for PK parameters to be generated.

Per Protocol (PP) Population: The PP population will exclude non -evaluable subjects and subjects with major protocol deviations thought to impact the ability to assess the effect of study treatment. The criteria for excluding subjects from the PP population will be specified in the Statistical Analysis Plan (SAP). All statistical tests will be conducted at the 2-sided,

0.05 level of significance and the point estimate of treatment differences and the associated 95% confidence interval (CI) will be derived.

The ITT population will be used for summary of demographic and baseline characteristics. Demographic characteristics (age, sex, ethnicity, race, etc.) and screening clinical characteristics (vital signs, physical examination, etc.) will be summarized using descriptive statistics (number of patients [n], mean, standard deviation [SD], median, minimum [min], and maximum [max]) for continuous variables and using counts and associated percentages for categorical variables. Baseline laboratory results will be summarized overall and by treatment arm using descriptive statistics. Additionally, the proportion of subjects on antifibrotic or not on antifibrotic therapy at the time of randomization for each treatment arm will be summarized.

7.2.2 Primary Endpoint Analyses

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature. No hypothesis testing is planned.

All safety analyses will be performed on the safety population. The analysis of safety endpoints, including TEAEs, AEs, SAEs, TRAEs and AEs of interest (coded using the Medical Dictionary for Regulatory Activities [MedDRA®]), will be summarized by System Organ Class, Preferred Terms, and their maximum severity based on CTCAE v5.0 grade for all treated subjects.

Laboratory data will be analyzed both quantitatively and qualitatively. The latter will be done via comparison of laboratory data to standard reference ranges. Values outside the reference range and values considered to be clinically relevant will be summarized. Clinical laboratory tests, physical examination, ECGs, and vital signs will be summarized or tabulated by treatment arm and visit and will also be presented in shift tables. Treatment groups will be compared descriptively with regard to distribution parameters as well as with

regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Clinical laboratory tests, physical examination, ECGs, and vital signs will be summarized or tabulated by treatment arm and visit and will also be presented in shift tables.

7.2.3 Secondary Endpoint Analyses

PK analysis will be performed for PK Population and no formal statistical analysis of PK data is planned. For all other endpoints, analysis will be performed on the ITT population.

Pharmacokinetic parameters will be summarized using arithmetic mean, percent coefficient of variation (%CV), standard deviation (SD), median, minimum, and maximum values, and number of observations.

Trough concentrations will be summarized by geometric means and geometric coefficients of variation (GCV) and will be plotted across time by treatment arm. A separate analysis plan and a separate analysis report will be prepared for the PK analyses, if applicable.

Some of the endpoints, such as FVC, DLCO and 6MWD will be analyzed by analysis of covariance (ANCOVA) with study treatment without the assumption on linearity, and baseline values as covariates. Missing data not due to indicators of acute IPF exacerbation or death will be imputed based on a multiple imputation method assuming missing not at random (MNAR) framework. Continuous secondary efficacy endpoints such as LCQ will be analyzed using a mixed model repeated measures (MMRM) with a random coefficient regression model. Fixed effects in the model will include treatment, time, and baseline values as covariates and random effects allowing for subject-specific intercepts and slopes.

Analysis will be performed to evaluate the efficacy of INS018_055 orally administered for up to 12 weeks of treatment on FVC decline in adult subjects with IPF compared to

placebo. The analysis will include the fixed, categorical effect of treatment at each visit, and the fixed continuous effects of baseline FVC at each visit. Visit will be treated as the repeated measure with an unstructured covariance structure used to model the within-patient measurements.

All statistical tests will be conducted at the 2-sided, 0.05 level of significance and the point estimate of treatment differences and the associated 95% confidence interval (CI) will be derived.

To evaluate the impact of INS018_055 orally administered on acute IPF exacerbations compared to placebo, analysis will be performed. Number of acute IPF exacerbations and hospitalizations from baseline up to Week 12 will be tabulated by treatment arm.

To evaluate the efficacy of INS018_055 orally administered for up to12 weeks of treatment to improve QoL and functional measures compared to placebo, the LCQ tool domain-specific scores and total score summed across the domains will be analyzed overall and by treatment arm. No adjustment of multiplicity for testing is performed for this study. Subgroup analysis may be performed for other medications for IPF.

7.2.4 Exploratory Endpoint Analyses

No formal statistical analysis is planned to evaluate change in IPF blood biomarkers of INS018_055 activity from baseline to Weeks 2, 4, 8 and 12. For biomarker population (with pre-dose baseline value, and at least one value after treatment initiated) , biomarker levels, change from baseline, percentage change from baselinewill be summarized using descriptive statistics including arithmetic mean, percent coefficient of variation (%CV), standard deviation (SD), median, minimum, and maximum values, and number of observations.

7.3 HANDLING MISSING DATA

In the primary analysis of all continuous endpoints, missing data will not be imputed. The mixed model will handle missing data based on a likelihood method under the "missing at random assumption". This means that patients with missing data would have behaved similarly to patients with observed data.

Missing or incomplete AE dates will be imputed. For example, missing data not due to indicators of acute IPF exacerbation or death may be imputed based on a multiple imputation method. Handling of missing data for secondary endpoints as well as for sensitivity analysis will be described in the SAP.

7.4 RANDOMIZATION

Patients will be randomized to one of the 4 treatment arms in a 1:1:1:1 ratio (INS018_055 30 mg QD, INS018_055 30 mg BID, INS018_055 60 mg QD, or placebo), with approximately15 subjects in each treatment arm to ensure a total of about 60 subjects completing the 12-week treatment period.

Randomization of patients to the treatment groups will be performed via IRT. This system will not have a cap on patients taking SoC antifibrotic treatment.

InSilico Medicine will arrange for the randomization and the packaging and labelling of study medication (INS018_055, placebo). Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

A sample size calculation based on statistical power considerations will not be performed. However, given an approximate sample size of 15 subjects per treatment arm, there exists a 90% probability of observing at least 1 AE if the true population rate is approximately 15%, which will be sufficient to assess the feasibility of safety parameters.

8 INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP) for both China and the U.S., relevant InSilico Medicine Standard Operating Procedures (SOPs), and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients, and is stored in the ISF.

8.1 STUDY APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of

the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The investigator or delegate must give a full explanation to study patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. Translation will be provided where needed.

The patient must be given sufficient time to consider participation in the study. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or his delegate must sign (or place a seal on) and date the informed consent form. If a study collaborator has given a supplementary explanation, the study collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for study quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. Continuous risk review and assessment may lead to adjustments in study conduct, study design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

8.3.1 Source Documents

For adverse events, an end date may not always be available (e.g., due to hospital discharge and later recovery, or change in treating physician), but should be recorded in the source if known.

For eCRF all data need to be derived from source documents, which need to be available on-site (this could be for example physician's notes in patient files, printouts, patient diaries).

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

Medical history, including number of years since IPF diagnosis, family history of IPF, clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and alcohol and substance use, that occurred prior to time of first dose of study drug should be reported as medical history on the General History and Baseline Conditions eCRF, including:

- Pulmonary hypertension
- Chronic obstructive pulmonary disease, i.e., COPD/emphysema
- Lung cancer
- Obstructive sleep apnea
- Pulmonary embolism
- Respiratory infections, including tuberculosis

- Cardiovascular disease and risk factors, including arrhythmias, cardiac failure or congestive heart failure, ischemic heart disease, cerebrovascular disease and stroke, peripheral artery disease systemic arterial hypertension, hypercholesterolemia/hyperlipidemia
- Participation in supervised pulmonary or cardiac rehabilitation programs
- Past surgical history

All medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a subject within 30 days prior to initiation of study treatment will be recorded on the eCRF. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded. History of anti-fibrotic therapy should also be documented since IPF was diagnosed (i.e., pirfenidone and nintedanib treatment, dose, duration of therapy, reasons for discontinuation, if applicable). Additionally, history of all COVID-19 vaccinations received in the past should be documented.

If it is determined that there will be central reading, copies of necessary source files will be provided to a vendor. Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g., patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

If the patient is not compliant with the protocol, any corrective action e.g., re-training must be documented in the patient file.

For the eCRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Adverse events and outcome events [onset date (mandatory), and end date (if available)]
- Serious adverse events [onset date (mandatory), and end date (if available)]

- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Patient related outcome worksheet completed by the patient and reviewed by the site.
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g., medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct Access to Source Data and Documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g., FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage Period of Records

Study sites must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer). The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

InSilico Medicine is responsible to fulfill their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook. Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

Personalized treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities.

8.5.1 Collection, storage, and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, and future use of biological samples and clinical data, in particular:

- The facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

8.6 STUDY MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent. The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").The "**Last Patient Last Treatment**" (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days

after LPLT at their site. Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol. **Temporary halt of the trial** is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it. **Suspension of the trial** is defined as an interruption of the trial based on a Health Authority request. The IEC/competent authority will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial to incorporate and consider all data in the report. The sponsor will submit China database a summary of the final trial results within one year from the end of a clinical trial as a whole.

8.7 ADMINISTRATIVE STRUCTURE OF THE STUDY

This study is sponsored by InSilico Medicine.

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A DSMB will be established. Members of the DSMB are physicians experienced in the treatment of the disease under investigation. The DSMB will evaluate the entire safety data and will meet on an ongoing basis during the course of the trial. The DSMB can receive urgent significant safety concerns for immediate evaluation. While DSMB members may be unblinded, measures are in place to ensure the blinding for everyone else involved in the trial. Regular DSMB meetings will be held at specified intervals. The DSMB will recommend continuation, modification or termination of the trial as detailed in the DSMB charter. DSMB recommendations as well as the final InSilico Medicine decision will be reported to the appropriate Regulatory Authorities (RAs)/Health Authorities (HAs), IRBs/ECs, and to investigators as requested by local law. The tasks and responsibilities of the DSMB are specified in a charter.

Relevant documentation on the participating (Principal) Investigators (e.g., their curricula vitae) will be filed in the ISF.

The investigators will have access to the InSilico Medicine portal to access documents provided by the sponsor.

InSilico Medicine has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to:

- Manage the trial in accordance with applicable regulations and internal SOPs
- Direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- Ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organization of the trial in the participating countries will be performed by the respective local or regional InSilico Medicine in accordance with applicable regulations and InSilico Medicine SOPs, or by a Contract Research Organization (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by InSilico Medicine according to InSilico Medicine SOPs. Bioanalysis of INS018_055 is done by sponsor or a delegated laboratory.

Tasks and functions assigned in order to organize, manage, and evaluate the trial are defined according to InSilico Medicine SOPs. A list of responsible persons and relevant local information can be found in the ISF.

An IRT vendor will be used in this trial. Details will be provided in the IRT Manual available in the ISF.

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10 APPENDICES

10.1 LCQ PRO TOOL

LEICESTER COUGH QUESTIONNAIRE

Appendix 1 : LEICESTER COUGH QUESTIONNAIRE © 2001

This questionnaire is designed to assess the impact of your cough on various aspects of your life. Read each question carefully and answer by CIRCLING the response that best applies to you. Please answer ALL questions, as honestly as you can.

1.	In the last 2 weeks, have you had chest or stomach pains as a result of your cough?						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
2.	In the last 2 weeks, have you been bothered by phlegm production when you cough?						
	1	2	3	4	5	6	7
	Every time	Most times	Several times	Sometimes	Occasionally	Rarely	Never
3.	In the last 2 weeks, have you been tired because of your cough?						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
4.	In the last 2 weeks, have you felt in control of your cough?						
	1	2	3	4	5	6	7
	None of the time	Hardly any of the time	A little of the time	Some of the time	A lot of the time	Most of the time	All of the time
5.	How often during the last 2 weeks have you felt embarrassed by your coughing?						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
6.	In the last 2 weeks, my cough has made me feel anxious						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
7.	In the last 2 weeks, my cough has interfered with my job, or other daily tasks						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
8.	In the last 2 weeks, I felt that my cough interfered with the overall enjoyment of my life						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
9.	In the last 2 weeks, exposure to paints or fumes has made me cough						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
10.	In the last 2 weeks, has your cough disturbed your sleep?						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
11.	In the last 2 weeks, how many times a day have you had coughing fits?						
	1	2	3	4	5	6	7
	All of the time (continuously)	Most times during the day	Several times during the day	Sometimes during the day	Occasionally through the day	Rarely	None
12.	In the last 2 weeks, my cough has made me feel frustrated						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
13.	In the last 2 weeks, my cough has made me feel fed up						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
14.	In the last 2 weeks, have you suffered from a hoarse voice as a result of your cough?						
	1	2	3	4	5	6	7
	All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time
15.	In the last 2 weeks, have you had a lot of energy?						
	1	2	3	4	5	6	7
	None of the time	Hardly any of the time	A little of the time	Some of the time	A lot of the time	Most of the time	All of the time

16. In the last 2 weeks, have you worried that your cough may indicate a serious illness?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

17. In the last 2 weeks, have you been concerned that other people think something is wrong with you because of your cough?

1	2	3	4	5	6	7
All of the time	Most of the time	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

18. In the last 2 weeks, my cough has interrupted conversations or telephone calls

1	2	3	4	5	6	7
Every time	Most times	A lot of the time	Some of the time	A little of the time	Hardly any of the time	None of the time

19. In the last 2 weeks, I feel that my cough has annoyed my partner, family or friends

1	2	3	4	5	6	7
Every time I cough	Most times when I cough	Several times when I cough	Sometimes when I cough	Occasionally when I cough	Rarely	Never

Thank you for completing this questionnaire.

10.2 DLCO

At Visit 1, DLCO must fulfil the following criteria: Within range 25% - 80% predicted of normal; corrected for Hb

For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the method used must be in compliance with the ATS/ERS guideline on DLCO measurements [Graham 2017], and the prediction formula appropriate for that method. Raw data (gas mixture, equation for the prediction of normal, further adjustments made if so), must be traced.

Predicted DLCO corrected for haemoglobin (Hb) expressed in g x dL^{-1} [Graham 2017], can be calculated as:

Males: Predicted DLCO corrected for Hb = Predicted DLCO x [1.7Hb/(10.22+Hb)]
Females: Predicted DLCO corrected for Hb= Predicted DLCO x [1.7Hb/(9.38+Hb)]

For decision on inclusion/exclusion, DLCO results from visit 1 will be corrected for hemoglobin by the site.

For analysis of the trial data, DLCO results will be corrected for hemoglobin by central data management. This means that the site has to enter the DLCO results without hemoglobin correction in the eCRF, at Visit 2 and Visit 6.

The average of DLCOs will be calculated in the EDC. The predicted DLCO, % predicted DLCO, and corrected % predicted DLCO will be calculated by statistician programmer using an equation to be confirmed, e.g. CRAPO or GLI.

There should be $\geq$ 2 acceptable tests that meet the repeatability requirement of either being within 3 mL CO (Standard Temperature and Pressure, Dry - STPD)•min-1 •mmHg-1 (or 1 mmol•min-1•kPa-1) of each other or within 10% of the highest value.

10.3 6MWD

Table 10. The Borg Scale CR10

0	Nothing at all	
0.3		
0.5	Extremely weak	Just noticeable
0.7		
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	Extremely strong	"Maximal"
11		
∿		
●	Absolute maximum	Highest possible

Borg CR10 Scale®
© Gunnar Borg, 1982, 1998, 2004
English

Borg CR10 Scale®
© Gunnar Borg, 1982, 1998, 2004
English

10.4 TIME SCHEDULING FOR PK BLOOD SAMPLING

Table 11. Time Schedule for PK Blood Sampling

Visit	Week	Time Point	**PK for INS018_055**	PD Markers	Pirfenidone, nintedanib
2	0	Pre-dose	-0:45	x	x
		Drug administration morning dose	0:00		
		Post-dose	+0:15 ± 5 min +0:30 ± 5 min +1:00 ± 5 min +2:00 ± 5 min +4:00 ± 5 min +6:00 ± 10 min +24:00 ± 30 min prior to next dosing		
3	2	Pre-dose	-0:45	x	x
		Drug administration morning dose	0:00		
4	4	Pre-dose	-0:45	x	x
		Drug administration morning dose	0:00		
5	8	Pre-dose	-0:45	x	x
		Drug administration morning dose	0:00		
6	12	Pre-dose	-0:45	x	x
		Drug administration morning dose	0:00		
		Post-dose	+0:15 ± 5 min +0:30 ± 5 min +1:00 ± 5 min		

			+2:00 ± 5 min +4:00 ± 5 min +6:00 ± 10 min +24:00 ± 30 min +48:00 ± 60 min		

10.5 ELIGIBILITY CONFIRMATION OF IPF DIAGNOSIS

Eligible refers to subjects with a clinical diagnosis of IPF based on the 2022 ATS/ERS/JRS/ALAT Clinical Practice Guideline on the diagnosis of IPF as confirmed by central review on chest HRCT scan taken within 12 month of Visit 1 and if available surgical lung biopsy. If HRCT is equivocal, surgical lung biopsy results may be used.

All chest HRCTs will be confirmed by central review based on the recent 2022 ATS/ERS/JRS/ALAT Clinical Practice Guideline on the diagnosis of IPF. Patients with a confirmed HRCT pattern qualifying as UIP or probable UIP are eligible for participation and are not required to have a surgical lung biopsy in the appropriate clinical context for the diagnosis of IPF.

Patients clinically suspected to have IPF with an HRCT pattern indeterminate for UIP, or suggesting an alternative diagnosis require historical (i.e., not taken for the purpose of this trial) surgical lung biopsy which will be reviewed locally (by the investigator/local histopathologist). In these patients, specific combinations of HRCT patterns and histopathology patterns may still allow a diagnosis of IPF based on the 2022 ATS/ERS/JRS/ALAT Clinical Practice Guideline on the diagnosis of IPF. E.g., An HRCT pattern of "indeterminate for UIP" in combination with a surgical lung biopsy with a histopathology pattern of “UIP or probable UIP” could qualify for inclusion.

Appropriate documentation at site for these cases is required. Copies of the original, histopathological assessments and resulting diagnosis are required in patient files.

Figure 2. IPF Diagnosis on the Basis of HRCT and Biopsy Patterns (2022 ATS/ERS/JRS/ALAT Clinical Practice Guideline)

IPF suspected*		Histopathology pattern†			
		UIP	Probable UIP	Indeterminate for UIP or biopsy not performed	Alternative diagnosis
HRCT pattern	UIP	IPF	IPF	IPF	Non-IPF dx
	Probable UIP	IPF	IPF	IPF (Likely)‡	Non-IPF dx
	Indeterminate	IPF	IPF (Likely)‡	Indeterminate§	Non-IPF dx
	Alternative diagnosis	IPF (Likely)‡	Indeterminate§	Non-IPF dx	Non-IPF dx

dx = diagnosis; UIP = usual interstitial pneumonia.
*"Clinically suspected of having IPF" is defined as unexplained patterns of bilateral pulmonary fibrosis on chest radiography or chest computed tomography, bibasilar inspiratory crackles, and age > 60 years. Middle-aged adults (>40 and <60 yr old) can rarely present with otherwise similar clinical features, especially in patients with features suggesting familial pulmonary fibrosis. †Diagnostic confidence may need to be downgraded if histopathological assessment is based on transbronchial lung cryobiopsy given the smaller biopsy size and greater potential for sampling error compared with surgical lung biopsy. ‡IPF is the likely diagnosis when any of the following features are present: 1) moderate to severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in four or more lobes, including the lingula as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man >50 years old or in a woman >60 yr old, 2) extensive (>30%) reticulation on HRCT and age > 70 yr, 3) increased neutrophils and/or absence of lymphocytosis in BAL fluid, and 4) multidisciplinary discussion produces a confident diagnosis of IPF. §Indeterminate for IPF 1) without an adequate biopsy remains indeterminate and 2) with an adequate biopsy may be reclassified to a more specific diagnosis after

10.6 CREATINE CLEARANCE

Table 12. Calculation of GFR CKD-EPI

Formula	Units	Decimal Places
Conventional **Black formulas** Female with a serum creatinine value of ≤0.7 mg/dL 166 x (Serum Creatinine (mg/dL) / 0.7) $^{-0.329}$ x (0.993)^{age} Female with a serum creatinine value of >0.7 mg/dL 166 x (Serum Creatinine (mg/dL) / 0.7) $^{-1.209}$ x (0.993)^{age}	mL/min/1.73m^2	0

Male with a serum creatinine value of ≤0.9 mg/dL 163 x (Serum Creatinine (mg/dL) / 0.9) $^{-0.411}$ x (0.993)^{age} Male with a serum creatinine value of >0.9 mg/dL 163 x (Serum Creatinine (mg/dL) / 0.9) $^{-1.209}$ x (0.993)^{age}		
Conventional **White, American Indian, Alaska Native, Asian, Native Hawaiian, Other Pacific Islander, Other formulas:** Female with a serum creatinine value of ≤0.7 mg/dL 144 x (Serum Creatinine (mg/dL) / 0.7) $^{-0.329}$ x (0.993)^{age} Female with a serum creatinine value of >0.7 mg/dL 144 x (Serum Creatinine (mg/dL) / 0.7) $^{-1.209}$ x (0.993)^{age} Male with a serum creatinine value of ≤0.9 mg/dL 141 x (Serum Creatinine (mg/dL) / 0.9) $^{-0.411}$ x (0.993)^{age} Male with a serum creatinine value of >0.9 mg/dL 141 x (Serum Creatinine (mg/dL) / 0.9) $^{-1.209}$ x (0.993)^{age} Creatinine in mg/dL is rounded to 2 decimal places prior to applying the formula.	mL/min/1.73m^2	0
SI Serum creatinine in µmol/L will be rounded to zero decimal place and converted to mg/dL by multiplying by 0.01131. This creatinine value in mg/dL will be rounded to 1 decimal place. This creatinine result will be used in the GFR Conventional formulas listed above.		
Limitations/Special Notes:	Age is truncated to a whole number prior to performing the calculation.	

10.7 EQUIVALENT DOSES OF CORTICOSTEROIDS

Table 13. Equivalent Doses of Corticosteroids

Steroid	Equivalent (mg)	Conversion Factor
Prednisone	5	x 1
Prednisolone	5	x 1
Triamcinolone	4	x 1.25
6-Methylprednisolone	4	x 1.25
Dexamethasone	0.75	x 6.7
Betamethasone	0.75	x 6.7
Fluocortalon	5	x 1

Cloprednol	3.75 -5	x 1.0 -1.5
Deflazacort	6	x 0.8
Cortisol (hydrocortisone	20	x 0.25
Cortisone	25	x 0.20

10.8 RESTRICTED MEDICATIONS

Lists of medications with CYP3A4/CYP1A2 inhibitory activity can be found in Table 14. The lists are not exhaustive and will not be updated during the course of the study. Investigators are advised to verify product labeling/information.

Table 14. Examples of Clinical Inhibitors and Inducers for CYP-Mediated Metabolism

CYP Enzyme	Strength	Examples*
CYP3A4 Inhibitors	Strong	cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and ombitasvir (and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole
	Moderate	aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, grapefruit juice, imatinib, isavuconazole, tofisopam, verapamil
CYP3A Inducers	Strong	apalutamide, carbamazepine, enzalutamide, ivosidenib, lumacaftor, mitotane, phenytoin, rifampin, St. John's wort
	Moderate	bosentan, cenobamate, dabrafenib, efavirenz, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, sotorasib
CYP1A2 Inhibitors	Strong	ciprofloxacin, enoxacin, fluvoxamine
	Moderate	methoxsalen, mexiletine, oral contraceptives, vemurafenib
CYP1A2 Inducers	Strong	---
	Moderate	phenytoin, rifampin, smoking, teriflunomide

*U.S. FDA. https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3. Accessed Nov 3, 2022.

Protocol Errata

Protocol No.: INS018-055-003
Version of Protocol: 4.0 (Amendment Version: 3.0)
Date of Protocol: 02Feb2024

The following error has been identified in the protocol document.

Item	Location	Incorrect	Correct
Header Date	Pages 41 - 108	02Aug2024	02Feb2024

This erratum is for record-keeping purposes only and does not impact on the study's scientific integrity or results.

InSilico Medicine Hong Kong Limited Unit 310, F3, Building 8W, Phase 2, Hong Kong Science Park, Pak Shek Kok, New Territories, Hong Kong

Date: 06 Nov 2025