STUDY PROTOCOL MTX-463-I201

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of MTX-463 in Participants with Idiopathic Pulmonary Fibrosis (IPF)

Short Title: Evaluation of MTX-463 in Participants with Idiopathic Pulmonary Fibrosis (IPF)

Sponsor Name and Address	Mediar Therapeutics 20 Overland Street Suite 520 Boston MA 02215 PPD PPD
Regulatory Agency Identifier Number(s)	IND: 170372 EU CT Number: 2025-521278-32
Protocol Number	MTX-463-I201
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Previous Versions and Dates	Original Protocol, Version 1.0, 05 March 2025 Version 1.1, 24 July 2025 (UK-specific amendment Version 1.2, 23 September 2025 (EU-specific amendment)

This study will be conducted in compliance with the protocol and in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline and all applicable regulatory requirements.

Confidentiality Statement

The information contained in this document is confidential and may not be used, divulged, published, or otherwise disclosed to others except to the extent necessary to obtain approval from an Institutional Review Board or Independent Ethics Committee, regulatory authority, or as required by law. Persons to whom this document is disclosed may not disseminate this document or the information it contains without the prior written permission of Mediar Therapeutics, Inc.

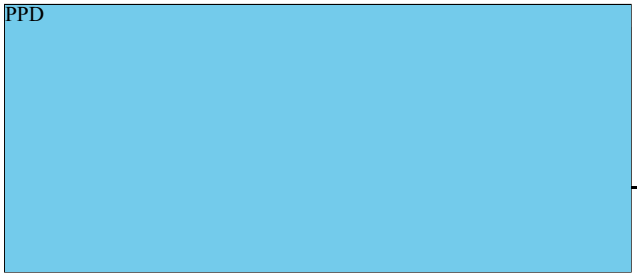
Sponsor Signature Page

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I, the undersigned, have reviewed and approve the protocol for this clinical study. I agree to conduct the study in accordance with the clinical study protocol, Good Clinical Practice, and the applicable laws and regulations of the countries in which the study takes place.

Name of Sponsor(s) or Sponsor's Responsible Medical Officer



15-Dec-2025

Date

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2. LIST OF ABBREVIATIONS

Term	Definition
ADA	antidrug antibody
ADL	activities of daily living
AE	adverse event
ATS	American Thoracic Society
BMI	body mass index
CA-19-9	cancer antigen 19-9
CA-125	cancer antigen 125
CCL2	chemokine ligand 2
CCL18	chemokine ligand 18
C_{max}	maximum concentration
CRA	clinical research associate
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTX	C-terminal cross-linked telopeptide of type I collagen
CXCL13	chemokine ligand 13
CYFRA 21-1	cytokeratin 19 fragment
DLCO	diffusing capacity of the lungs for carbon monoxide
DSMB	data safety monitoring board
ECM	extracellular matrix
eCRF	electronic case report form
EOS	end of study
EOT	end of treatment
ERS	European Respiratory Society
ET	early termination
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
FVC_{pp}	percent predicted forced vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus

Term	Definition
HRCT	high-resolution computed tomography
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IL-6	interleukin-6
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IV	intravenous
KL-6	Krebs von den Lungen-6
LPLV	last participant last visit
L-PF	Living with Pulmonary Fibrosis
MAD	multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MMP-7	matrix metalloproteinase-7
MMRM	mixed-effect model for repeated measures
NCI	National Cancer Institute
P1NP	procollagen type 1 N-terminal propeptide
PAI-1	plasminogen activator inhibitor 1
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
POSTN	periostin
pp	percent predicted
PRO-C3	propeptide of type 3 collagen
PRO-C6	propeptide of type 6 collagen
Q2W	once every 2 weeks
Q4W	once every 4 weeks
RBC	red blood cells
SAD	single ascending dose

Term	Definition
SAE	serious adverse event
SAP	statistical analysis plan
sICAM1	soluble intercellular adhesion molecule 1
SMAD	small mother against decapentaplegic
SoA	schedule of assessments
SP-D	surfactant protein D
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TIMP-1	tissue inhibitor of metalloproteinases 1
TNC	tenascin C
TRAE	treatment-related adverse event
WISP1	WNT-inducible signaling pathway protein 1

3. PROTOCOL SUMMARY

3.1 Synopsis

Name of Sponsor/Company	Mediar Therapeutics
Name of Finished Product	MTX-463
Title of Study	A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of MTX-463 in Participants with Idiopathic Pulmonary Fibrosis (IPF)
Short Title	Evaluation of MTX-463 in Participants with Idiopathic Pulmonary Fibrosis (IPF)
Study Center(s)	Global
Phase of Development	2a

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the effect of MTX-463 on the change from Baseline in forced vital capacity (FVC)	• Change from Baseline to Week 24 in FVC
Secondary	
• To assess the safety and tolerability of MTX-463 in participants with IPF	• Incidence, seriousness, and severity of treatment-emergent adverse events (TEAEs) and treatment-related adverse events (TRAEs); and incidence of dose interruptions and discontinuations • Clinically significant findings on physical examinations, vital signs, and clinical laboratory tests
• To assess the effect of MTX-463 on the change from Baseline in the percent predicted FVC (FVC_{pp})	• Change from Baseline to Week 24 in the FVC_{pp}
• To collect sparse pharmacokinetics (PK) of MTX-463 in participants with IPF	• Sparse PK profiles will be evaluated by population PK analyses
Exploratory	
• To assess the effect of MTX-463 on the change from Baseline in FVC in participants on concomitant nintedanib, pirfenidone, or nerandomilast	• Change from Baseline to Week 24 in FVC in participants on concomitant nintedanib, pirfenidone, or nerandomilast
• To assess the effect of MTX-463 on the change from Baseline in FVC in participants not on concomitant nintedanib, pirfenidone, or nerandomilast	• Change from Baseline to Week 24 in FVC in participants not on concomitant nintedanib, pirfenidone, or nerandomilast
• To assess the effect of MTX-463 on the change from Baseline in the Living with Pulmonary Function (L-PF) Questionnaire total score	• Change from Baseline to Week 24 in L-PF total score
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CCI	
• To assess the effect of MTX-463 on the change from Baseline in percent predicted diffusing capacity of the lungs for carbon monoxide (DLCO)	• Change from Baseline to Week 24 in percent predicted DLCO
• To evaluate the time to disease progression as determined by change in FVC, IPF-related changes, or death	• Time to disease progression with progression being defined as ≥10% decline in FVC_{pp} from Baseline, IPF-related hospitalization, or death
• To assess the development of antidrug antibodies (ADA) against MTX-463	• Presence, titer, and impact of ADA
• To assess the effect of MTX-463 on biomarkers of IPF	• Change from Baseline to Week 24 in the PROLIFIC panel of 12 biomarkers (matrix metalloproteinase-7 [MMP-7], surfactant protein D [SP-D], Krebs von den Lungen-6 [KL-6], plasminogen activator inhibitor 1 [PAI-1], cancer antigen 19-9 [CA-19-9], cytokeratin 19 fragment [CYFRA 21-1], chemokine ligand 13 [CXCL13], soluble intercellular adhesion molecule 1 [sICAM1], chemokine ligand 18 [CCL18], periostin (POSTN), cancer antigen 125 [CA-125], and tenascin C [TNC]) • Change from Baseline to Week 24 in tissue inhibitor of metalloproteinase-1 [TIMP-1], chemokine ligand 2 [CCL2], propeptide of type 3 collagen [Pro-C3], propeptide of type 6 collagen [Pro-C6], C7M, and interleukin-6 (IL-6)
• To assess the effect of MTX-463 on biomarkers of bone remodeling	• Change from Baseline to Week 24 on procollagen type 1 N-terminal propeptide [P1NP] and C-terminal cross-linked telopeptide of type 1 collagen [CTX]

Methodology	Participants with IPF who meet the study's inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to receive MTX-463 or a matching placebo by intravenous (IV) infusion. Approximately 50% of the study population will be on a background of approved IPF therapy (pirfenidone, nintedanib, or nerandomilast), and randomization will be stratified by whether participants are on background therapies or not. Participants randomized to the MTX-463 arm of the study will receive a loading dose of CCI mg/kg at their Baseline Visit (Day 0), followed by 5 infusions of CCI mg/kg once every 4 weeks (Q4W) starting at Study Week 4 (Weeks 4, 8, 12, 16, and 20). The End-of-Treatment visit will occur at Week 24, 4 weeks after the final infusion; and a final Safety Follow-Up Visit will occur at Week 28, 8 weeks after the final infusion.

	Assessments of FVC will occur at Screening, Baseline, and at all subsequent treatment visits up to and including Week 24. A high-resolution computerized tomography (HRCT) of the lungs will occur at Screening unless it has been performed in the 90 days prior to Screening and supports the diagnosis of IPF. Alternatively, the diagnosis of IPF is acknowledged if made on a lung biopsy. All HRCTs, including those performed prior to Screening, will be centrally read and confirmed to meet the diagnostic criteria for IPF by the central reader. L-PF assessments will be performed at Baseline and Week 24. Participants will have blood drawn for safety assessment and to assess WISP1 levels at Baseline and every 4 weeks throughout the study. Blood will be drawn for serum PK analyses relative to the first and last doses of MTX-463.
Number of Planned Participants	Approximately 164 study participants, globally
Study Population	Participants with IPF
Criteria for Inclusion	1. Participants with IPF of any gender ≥40 years of age at time of signing the informed consent 2. Able to understand the study and provide signed, written informed consent 3. Able to read and understand the language of the informed consent and other study related materials 4. Meet the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), or Latin American Thoracic Association (ALAT) 2019 criteria for the diagnosis of IPF[1]; diagnosed with IPF within 7 years of Screening 5. If a participant is on treatment with pirfenidone, nintedanib, or nerandomilast, the dose of the medication must be stable for ≥90 days prior to Screening, and there should be a plan to maintain the same dose throughout the study Treatment Period. Use of any of these 3 agents in combination with each other is not permitted. 6. If a participant was on treatment with nintedanib, pirfenidone, or nerandomilast and the agent has been discontinued, this must have occurred ≥30 days prior to Screening. At Screening, there must also be no plan to start any of these medications for the duration of the study. Participants newly diagnosed with IPF who, in the judgment of the treating physician, are considered in need of treatment with nintedanib, pirfenidone, or nerandomilast should not defer standard of care treatment and should be excluded from the study. 7. FVC of ≥45 percent predicted (pp) at Screening 8. DLCO of ≥25 pp at Screening 9. Willing and able to complete all protocol-required study visits and procedures 10. Female participants of childbearing potential must have a negative serum pregnancy test at Screening and must agree to use and follow medically approved, highly effective methods of contraception during treatment and until 5 half-lives or 125 days after the last dose of study drug, whichever is longer (see Appendix 3 for details).

	11. Male participants with female partners of childbearing potential must use condoms during the treatment and until 5 half-lives or 125 days after the last dose of study drug, whichever is longer (see Appendix 3 for details).
Criteria for Exclusion	1. Acute exacerbation of IPF within 6 months of Screening or during the Screening Period 2. Forced expiratory volume in 1 second (FEV1)/FVC ratio of < 0.7 at Screening 3. Requirement for continuous supplemental oxygen. Intermittent supplemental oxygen use (e.g., during exercise or sleep) is permitted 4. Expected to receive a lung transplant within the study duration 5. Current active bacterial infection or use of antibiotics for suspected lung infection in the 30 days prior to Screening 6. Planned surgery within the study duration 7. Clinically significant pulmonary hypertension 8. Use of immunosuppressive therapy (excluding corticosteroids). If previously on such agents, they should have been discontinued for at least 5 half-lives or 90 days, whichever is longer, prior to Screening. 9. Use of systemic corticosteroids (prednisone or equivalent) at a dose >10 mg once daily within 30 days of Screening 10. Currently smoking or vaping 11. Current known malignancy, or history of cancer, or lymphoproliferative disorder other than non-melanomatous skin cancers, within 2 years of Screening 12. Current infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) 13. Currently pregnant, breast feeding, or planning to conceive for the length of the study 14. History of severe depression, psychosis, or suicidal ideation, as determined by the Investigator, within 2 years of Screening 15. Any clinically significant disease or laboratory abnormality detected at Screening that might interfere with a participant's ability to complete the study, on-study evaluations, or participant safety 16. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2× upper limit of normal (ULN) at Screening 17. Presence of interstitial lung disease due to any cause other than IPF, clinically significant cardiovascular disease, or any other concurrent active medical condition determined by the Investigator to interfere with the participant's ability to complete the study 18. Known allergy to MTX-463 or any of its excipients, or a history of a prior allergic reaction to a monoclonal antibody therapeutic 19. Any prior use of MTX-463 or other therapy targeting WISP1 20. Any other concurrent experimental agent or an active part of any other clinical study, unless they have stopped taking the investigational product at least 5 half-lives or 30 days before Screening, whichever is longer

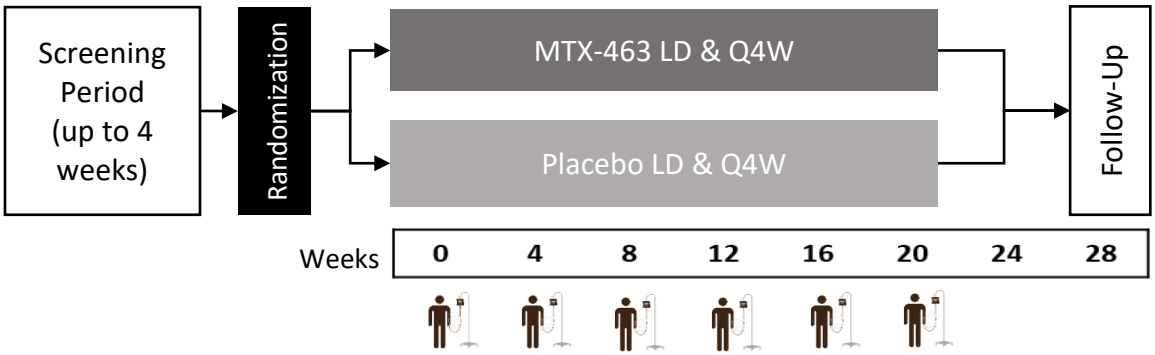
Test Product	MTX-463
Doses	MTX-463 CCI-mg/kg loading dose on Day 0 (Week 0) followed by CCI mg/kg Q4W maintenance doses on Weeks 4, 8, 12, 16, and 20
Mode of Administration	IV infusion
Concurrent Control	Matched placebo
Duration of Treatment	The maximum duration of participation for an individual in the study will be 32 weeks, which includes a 4-week Screening Period, a 24-week Treatment Period (including the End-of-Treatment visit), and a 4-week Safety Follow-Up Period.
Statistical Methods	The Statistical Analysis Plan (SAP) will specify the statistical methods and display formats that will be used for summarizing and reporting the study results. Intercurrent events and their handling strategies will be detailed in the SAP. The statistical analyses for various assessment parameters are described below. The full statistical analyses are detailed in the SAP. *Sample Size* A sample size of approximately 164 participants, with approximately 82 participants per treatment arm, was selected based on the following assumptions: CCI [redacted] CCI [redacted] CCI [redacted] CCI [redacted] • Expected dropout rate of 10% • 2-sided alpha level of 0.05 and 80% power *Analysis Sets* The Safety Analysis Set will consist of all participants who received at least one dose of study drug (MTX-463 or placebo). This analysis set will be used for all safety analyses. The Efficacy Analysis Set will consist of all participants who received at least one dose of study drug and had at least one post-treatment FVC assessment. The PK Analysis Set will consist of participants who have received at least one dose of MTX-463 or placebo, and who have measurable serum concentration data. This analysis set will eventually be used in subsequent population PK analyses. *Safety Analyses* All safety results will be summarized using descriptive statistics for the placebo control and each of the MTX-463 dose levels studied using the Safety Analysis Set. TEAEs are defined as adverse events (AEs) with onset after the administration of the first dose of study treatment or preexisting conditions that worsen after administration of the first dose of study treatment. TEAEs, including TRAEs, TEAEs by maximum severity, and

	serious TEAEs, will be summarized. Listings of all AEs, serious TEAEs, fatal TEAEs, and TEAEs leading to discontinuation will be provided. Descriptive statistics for vital signs, physical examinations, and clinical laboratory parameters, including change from Baseline when applicable, will be summarized by timepoint. The incidence of clinically significant changes in selected laboratory parameters also will be summarized. *Efficacy Analyses* Changes from Baseline in FVC will be estimated using a mixed-effect model for repeated measures analysis. The model will include fixed effects for treatment, scheduled visits, treatment-by-visit interactions, and concomitant nintedanib, pirfenidone, or nerandomilast (yes/no) as categorical variables, along with Baseline FVC and Baseline FVC by-visit interaction as continuous covariates. Changes from Baseline in FVC_{pp} will be estimated using the same model used for the primary efficacy model. Time to disease progression (with progression defined as ≥10% decline in FVC_{pp} from Baseline, IPF-related hospitalization, or death) will be estimated using the Kaplan-Meier method. *Pharmacokinetic Analyses* Serum concentrations for MTX-463 will be listed and summarized using descriptive statistics. Sparse PK samples will be used to explore any relationships between MTX-463 exposure and clinical response, pharmacodynamic (PD) endpoints, AEs, and covariates, as data permit. These data will be analyzed together with PK data from other clinical studies for population PK analyses, as appropriate. *ADA Analyses* Serum sample results will be summarized for presence, titer, and impact of ADA, as feasible. *Exploratory Analyses* For participants with and without concomitant nintedanib, pirfenidone, or nerandomilast, change from Baseline in FVC will be estimated separately using a mixed-effect model similar to the primary efficacy analysis model. Changes in DLCO across time will be estimated using descriptive statistics. Change from Baseline in L-PF scores will be estimated in the treatment groups using analysis of variance techniques.

	Fibrosis Biomarkers and Pharmacodynamic Analyses Participants will be assessed for exploratory PD and fibrosis biomarkers in the serum. Descriptive summary statistics by timepoint will be used to describe the following: CCI [redacted] CCI [redacted] CCI [redacted] • Change from Baseline in TIMP-1, CCL2, Pro-C3, Pro-C6, C7M, and IL-6 levels • Change from Baseline in the PROLIFIC panel of 12 biomarkers (MMP-7, SP-D, KL-6, PAI-1, CA-19-9, CYFRA 21-1, CXCL13, sICAM1, CCL18, POSTN, CA-125, and TNC) • Change from Baseline in bone remodeling biomarkers P1NP and CTX

3.2 Study Schema

Figure 1: MTX-463-I201 Study Design



Abbreviations: LD = loading dose; Q4W = every 4 weeks.

3.3 Schedules of Assessments

Table 1: Schedule of Assessments

	Screening[a]	On Treatment							Follow-Up
Day	**-28 to -1**	**0 (Week 0) (Baseline)**	**28 (Week 4)**	**56 (Week 8)**	**84 (Week 12)**	**112 (Week 16)**	**140 (Week 20)**	**168 (Week 24) (EOT/ ET)**	**196 (Week 28) (EOS)**
Visit window			**(±3 days)**						
Informed consent	X								
Inclusion/exclusion review	X	X							
Demographics	X								
Medical history and medications history	X	X							
Randomization[b]	X[b]								
Physical examination[c]	X	X	X	X	X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X	X	X
Height, weight, and BMI calculation[e]	X	X							X
Clinical laboratory tests[f]	X	X	X	X	X	X	X	X	X
Serology[g]	X								
Pregnancy test[h]	X	X	X	X	X	X	X	X	X
Study drug administration[i]		X	X	X	X	X	X		
Spirometry[j]	X	X	X	X	X	X	X	X	
DLCO[k]	X							X	
HRCT[l]	X								
L-PF assessment[m]		X						X	
PK sampling	Refer to Table 2 for sampling schedule.								
ADA[n]		X	X		X		X	X	X
WISP1 levels[o]		X	X	X	X	X	X	X	X
TIMP-1 levels		X	X	X	X			X	
CCL2 levels		X	X	X	X			X	
Pro-C3 levels		X	X	X	X			X	
Pro-C6 levels		X	X	X	X			X	
C7M levels		X	X	X	X			X	
IL-6 levels		X	X	X	X			X	
PROLIFIC biomarker levels[p]		X	X	X	X			X	

Table 1: Schedule of Assessments(Continued)

	Screening[a]	On Treatment							Follow-Up
Day	**-28 to -1**	**0 (Week 0) (Baseline)**	**28 (Week 4)**	**56 (Week 8)**	**84 (Week 12)**	**112 (Week 16)**	**140 (Week 20)**	**168 (Week 24) (EOT/ ET)**	**196 (Week 28) (EOS)**
Visit window			**(±3 days)**						
P1NP levels		X	X	X	X			X	
CTX levels		X	X	X	X			X	
Concomitant medications	X	X	X	X	X	X	X	X	X
Assessment of AEs[q]	X	X	X	X	X	X	X	X	X

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; BMI = body mass index; BP = blood pressure; CCL2 = chemokine ligand 2; CA-125 = cancer antigen 125; CA-19-9 = cancer antigen 19-9; CCL18 = chemokine ligand 18; CTCAE = Common Terminology Criteria for Adverse Events; CTX = C-terminal cross-linked telopeptide of type I collagen; CXCL13 = chemokine ligand 13; CYFRA 21-1 = cytokeratin 19 fragment; DLCO = diffusing capacity of the lungs for carbon monoxide; EOS = End of Study; EOT = End of Treatment; ET = early termination; FEV1 = forced expiration volume in 1 second; FVC = forced vital capacity; HRCT = high-resolution computed tomography; IL-6 = interleukin-6; IPF = idiopathic pulmonary fibrosis; KL-6 = Krebs von den Lungen-6; L-PF = Living with Pulmonary Fibrosis; MMP-7 = matrix metalloproteinase-7; NCI = National Cancer Institute; P1NP = procollagen type 1 N-terminal propeptide; PAI-1 = plasminogen activator inhibitor 1; PK = pharmacokinetics; POSTN = periostin; Pro-C3 = propeptide of type 3 collagen; Pro-C6 = propeptide of type 6 collagen; sICAM1 = soluble intercellular adhesion molecule 1; SoA = Schedule of Assessments; SP-D = surfactant protein D; TIMP-1 = tissue inhibitor of metalloproteinases 1; TNC = tenascin C; WISP1 = WNT-inducible signaling pathway protein 1.

Note: All protocol-specific assessments detailed in the above SoA (Table 1) are considered significant study procedures and require documentation of adequate training and delegation for clinical staff conducting assessments.

Note: Pre-dose assessments are to be conducted within 2 hours before dosing, when possible. All other timepoints are to be calculated from the start of infusion.

[a] Screening window is a maximum of 28 days.

[b] Participants will be randomized at a 1:1 ratio to either MTX-463 or matching placebo (See Section 6.5 for details). Eligible participants can be randomized any time from Day -2 to Day 0.

[c] A full physical examination will be conducted at Screening and Day 0 and will be symptom-directed at each subsequent visit.

[d] Vital signs should be taken pre-dose and will include BP, heart rate, respiratory rate, temperature, and pulse oximetry. BP and heart rate should be measured after the participant has been supine for at least 5 minutes. Vital signs should be measured prior to any PK blood draw.

[e] Height will only be measured at the Screening visit; weight will be measured at Screening, Baseline on Day 0, and Week 28 (Day 196 [±3 days]).

[f] See Section 9.2.5 for a list of hematological tests and the clinical chemistry panel to be assessed. A single repeat safety laboratory assessment will be permitted to confirm the initial result of Screening laboratory tests if the result is suspected to be incorrect.

[g] See Section 9.2.5 for a list of serological tests to be assessed. Results must be confirmed negative prior to Day 0 to randomize potential participants.

[h] For female participants of childbearing potential (see Appendix 3 for details), a Screening serum pregnancy test will be collected. For participants of childbearing potential, urine pregnancy test (only) will be collected at timepoints depicted in the SoA.

[i] Study drug (or matching placebo) will be administered by IV infusion over 75 minutes (±15 minutes) for the loading dose level and over 60 minutes (±15 minutes) for the maintenance dose level per the procedure outlined in the Pharmacy Manual. Participants should be observed for 15 minutes post-infusion to ensure safety. The end of infusion is documented upon completion of study drug infusion, not upon completion of the post-infusion line flush.

[j] Spirometry assessments will include FEV1 and FVC. Bronchodilator use (short- and long-acting) will not be permitted on the day of spirometry prior to the assessment.

[k] Same procedure and machine are required for assessing DLCO.

[l] An HRCT scan of the chest will be obtained at Screening if needed to confirm the diagnosis. All HRCTs, whether historical or obtained during Screening, will be centrally read to determine if the diagnostic criteria for IPF is met.

[m] Participants will complete the L-PF for Symptoms domain and for Impacts domain.

[n] ADA serum samples will be collected pre-dose at Baseline (Day 0) and Week 4 (Day 28 [±3 days]), Week 12 (Day 84 [±3 days]), Week 20 (Day 140 [±3 days]), Week 24 (Day 168 [±3 days]) and Week 28 (Day 196 [±3 days]).

[o] Serum samples for WISP1 levels will be collected at Baseline (within 2 hours before dosing on Day 0, when possible); at Weeks 4, 8, 12, 16, and 20 (Days 28, 56, 84, 112, and 140 [±3 days], respectively) (within 2 hours before dosing, when possible); and Week 24 (Day 168 [±3 days]) and Week 28 (Day 196 [±3 days]).

[p] The PROLIFIC panel of 12 biomarkers to be assessed will include MMP-7, SP-D, KL-6, PAI-1, CA-19-9, CYFRA 21-1, CXCL13, sICAM1, CCL18, POSTN, CA-125, and TNC.

[q] Adverse events will be graded using the NCI CTCAE, version 6.0.

Table 2: Sparse Pharmacokinetic Sampling Schedule of Assessments

Day	Screening -28 to -1	On Treatment 0 (Week 0) (Baseline)	28 (Week 4)	56 (Week 8)	84 (Week 12)	112 (Week 16)	140 (Week 20)	168 (Week 24) (EOT/ET)	Follow-Up 196 (Week 28) (EOS)
Visit window	[redacted]		**(±3 day)**						
Core PK Samples									
Pre-dose		X[a]							
15 minutes (±2 min)		X[a]					X[a]		
1 hr (±15 min)		X[a]					X[a]		
672 hr (±1 day) (28 days)[c]			X[a, c]					X[d]	
Additional PK Samples									
96 hr (±1 day) (4 days)		X[b]					X[b]		
336 hr (±1 day) (14 days)		X[b]					X[b]		

Abbreviations: ADA = anti-drug antibodies; EOS = End of Study; EOT = End of Treatment; ET = early termination; PK = pharmacokinetics; Q4W = every 4 weeks.
Note: Pre-dose assessments are to be conducted within 2 hours before dosing, when possible. All other timepoints are to be calculated from the start of infusion.
[a] For all participants while they are at the site for the dosing visit.
[b] At participating sites only.
[c] The 28-day samples should be collected before administration of the next dose, if applicable, given the Q4W dosing schedule.
[d] For participants who early terminate from the study, a PK sample should be collected at the ET visit, and all subsequent ADA and PK samples should be collected at all specified visits/timepoints, as feasible.

4. INTRODUCTION

4.1 Background Information

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive-fibrosing, interstitial lung disease of unknown cause. IPF and non-specific interstitial pneumonia (NSIP) comprise the group of chronic fibrosing, idiopathic interstitial pneumonias as classified by the American Thoracic Society-European Respiratory Society (ATS-ERS) in 2013[2]. IPF is characterized clinically by relatively non-specific symptoms, where participants primarily present with onset of dyspnea on exertion, non-productive cough, and inspiratory crackles on lung examination[3]. A primary element of diagnosis is the absence of symptoms indicating systemic disease. Radiological and histopathological features are highly similar to that of usual interstitial pneumonia (UIP)[4].

The prognosis of IPF is typically quite poor. IPF arises most commonly in participants over 50, with a median age of onset of 66. Participants experience worsening shortness of breath that leads to eventual respiratory failure, although the time to progress is highly variable from participant to participant. The life expectancy for a participant with IPF is 3 to 5 years following initial diagnosis[3].

Enhanced myofibroblast activation, extracellular matrix (ECM) deposition, and alveolar epithelial type II (ATII) cell dysfunction are thought to contribute to IPF pathogenesis, but the overall disease pathways at the cellular level are poorly understood[5]. Disease pathogenesis is thought to involve recurrent injuries to alveolar epithelium and may arise more commonly in individuals with genetic factors that may predispose them to the disease, followed by failure of alveolar re-epithelialization and post-injury repair[6]. Activated cells within the alveoli release cytokines and growth factors that promote the recruitment, proliferation, and differentiation of lung fibroblasts into myofibroblasts, leading to excessive collagen deposition, progressive scarring of the lung parenchyma, and irreversible loss of function[7,8].

Current evidence-based guidelines for treatment of IPF recommend the use of pirfenidone and nintedanib, two compounds with pleiotropic mechanisms of action; however, both drugs have limited efficacy in preventing disease progression and improving quality of life, and they are also associated with tolerability issues[9,10]. A third agent, nerandomilast, is approved in at least one jurisdiction. This agent slows progression of the disease but does not halt it[11]. Lung transplantation is the only cure for participants with IPF; but, due to age and comorbidities, this represents a realistic therapeutic option for only a minority of patients[12].

4.2 Investigational Drug Product Name

The investigational drug product name is MTX-463.

4.3 Study Rationale

MTX-463 is an immunoglobin G1 (IgG1) monoclonal antibody directed against WNT-inducible signaling pathway protein 1 (WISP1). WISP1 (aka cellular communication network factor 4 [CCN-4]) is a matricellular protein that appears to be upregulated locally in response to certain chronic diseases and malignancies. The increased production of WISP1 in the ECM leads to increased activation of myofibroblasts, with a resulting increase in collagen production and expansion of the ECM. Inhibition of WISP1 is postulated to restore myofibroblasts back to their quiescent state, with a decrease in collagen production and restoration of the expanded ECM back toward its normal state. As such, there is a rationale to evaluate systemic anti-WISP1

therapy such as MTX-463 as a potential treatment avenue for patients with IPF. The nonclinical data supporting the clinical development of MTX-463 is described in Section 4.4. A single-center study of MTX-463 to assess the safety, tolerability, pharmacokinetics (PK), immunogenicity (antidrug antibodies [ADAs]), and target engagement of MTX-463 in healthy adults was also conducted (Section 4.5).

4.4 Nonclinical Data

MTX-463 has undergone numerous nonclinical in vitro and in vivo studies. These studies include PK in rats, in vitro and in vivo pharmacology studies to examine the mechanism of MTX-463 and potential activity in disease models, 4- and 13-week Good Laboratory Practice (GLP) toxicology studies in both rats and cynomolgus monkeys, and a 6-month GLP toxicology study in rats. Data from the pharmacology studies are summarized below; details for nonclinical toxicology and PK are provided in the MTX-463 Investigator's Brochure (IB).

4.4.1 Pharmacology Studies

CCI

[redacted]

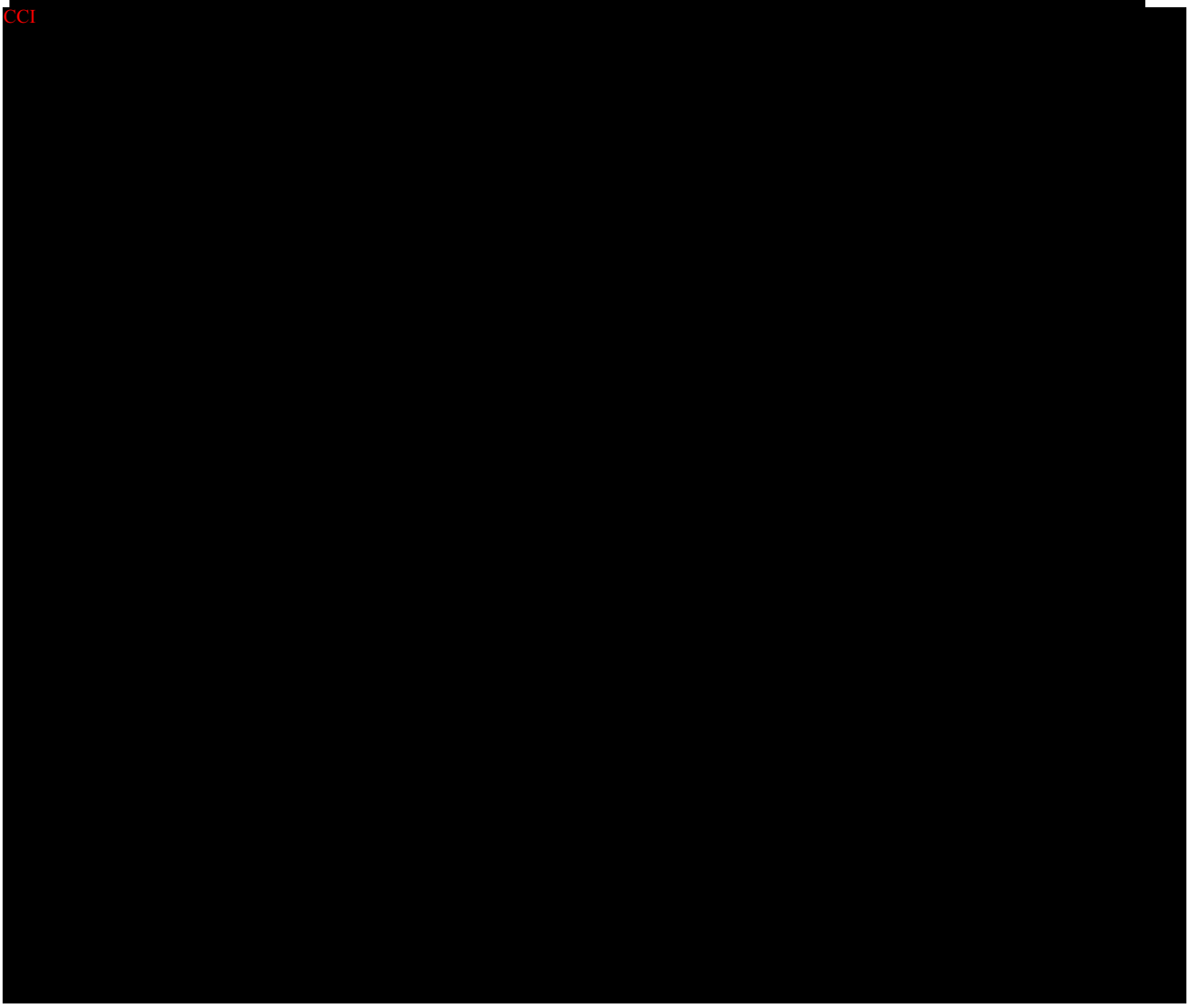
4.5 Clinical Data

MTX-463 was assessed in a first-in-human randomized, double-blind, dose-escalating study to determine the safety, tolerability, and PK in healthy participants. MTX-463 was administered as an intravenous (IV) infusion in doses of 4 mg/kg (Cohort 1), 8 mg/kg (Cohort 2), 16 mg/kg (Cohort 3), and 30 mg/kg (Cohort 4) in the single-ascending dose (SAD) portion of the study. In the multiple-ascending dose (MAD) portion, participants received a loading dose, followed

1 week later by their first maintenance dose, with a second maintenance dose 2 weeks after the first one (i.e., maintenance dosing once every 2 weeks [Q2W]). The doses administered were as follows: a 6.6 mg/kg loading dose and two 4 mg/kg Q2W maintenance doses (Cohort 1), a 13-mg/kg loading dose and two 8-mg/kg Q2W maintenance doses (Cohort 2), and a 27-mg/kg loading dose and two 16-mg/kg Q2W maintenance doses (Cohort 3). Few participants (10 in the MTX-463-treated group versus 3 in the placebo group) experienced treatment-emergent adverse events (TEAEs). There was no consistent pattern to the TEAEs reported. No serious TEAEs were reported in the study, and only 1 event led to early discontinuation.

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Target engagement was assessed by measuring both free and total levels of the target, WISP1, in serum. MTX-463 administration reduced the levels of circulating free WISP1 to below the limits of detection at all doses studied in both the SAD and MAD portions of the study and increased total WISP1 in a dose-proportional manner (ranging from 1378%-5136% increase), plateauing with repeat dose. Placebo administration had no effect on either free or total WISP1 levels.

4.6 Summary of Known and Potential Risks and Benefits to Participants

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted] Nonclinical toxicology studies of MTX-463 showed no adverse effects in the 4-week, 13-week, and 6-month terminal animals either in-life or at necropsy and histopathology. Participants may receive a clinical benefit from MTX-463, and some participants may progress. The information from this study may help other patients with IPF and more may be learned about the study drug as a possible new treatment for IPF.

Based on the available data, the risks associated with the use of MTX-463 are considered acceptable.

4.7 Selection of Doses in This Study

CCI [redacted]

Participants randomized to the MTX-463 arm of this study will receive an IV loading dose of CCI [redacted] mg/kg at their Baseline Visit (Day 0). Then, MTX-463 will be administered IV at a dose of CCI [redacted] mg/kg Q4W for 5 infusions. This study will examine the safety and clinical efficacy/activity of the CCI [redacted] mg/kg Q4W dose in participants with IPF.

4.8 Population Studied

This study will be conducted in participants with IPF.

5. PURPOSE, OBJECTIVES, AND ENDPOINTS

The purpose of this Phase 2, randomized, double-blind, placebo-controlled study is to assess the safety, tolerability, and efficacy of MTX-463 administered in participants with IPF. The objectives and endpoints of the study are as described in Section 5.1.

5.1 Objectives and Endpoints

Objective	Endpoint
Primary	
• To assess the effect of MTX-463 on the change from Baseline in forced vital capacity (FVC)	• Change from Baseline to Week 24 in FVC
Secondary	
• To assess the safety and tolerability of MTX-463 in participants with IPF	• Incidence, seriousness, and severity of TEAEs and treatment-related adverse events (TRAE); and incidence of dose interruptions and discontinuations • Clinically significant findings on physical examination, vital signs, and clinical laboratory tests
• To assess the effect of MTX-463 on the change from Baseline in the percent predicted FVC (FVC_{pp})	• Change from Baseline to Week 24 in the FVC_{pp}
• To collect sparse PK of MTX-463 in participants with IPF	• Sparse PK profiles will be evaluated by population PK analyses
Exploratory	
• To assess the effect of MTX-463 on the change from Baseline in FVC in participants on concomitant nintedanib, pirfenidone, or nerandomilast	• Change from Baseline to Week 24 in FVC in participants on concomitant nintedanib, pirfenidone, or nerandomilast
• To assess the effect of MTX-463 on the change from Baseline in FVC in participants not on concomitant nintedanib, pirfenidone, or nerandomilast	• Change from Baseline to Week 24 in FVC in participants not on concomitant nintedanib, pirfenidone, or nerandomilast
• To assess the effect of MTX-463 on the change from Baseline in the Living with Pulmonary Fibrosis (L-PF) Questionnaire total score	• Change from Baseline to Week 24 in L-PF total score
CCI [redacted]	

Objective	Endpoint
• To assess the effect of MTX-463 on the change from Baseline in percent predicted diffusing capacity of the lungs for carbon monoxide (DLCO)	• Change from Baseline to Week 24 in percent predicted DLCO
• To evaluate the time to disease progression as determined by change in FVC, IPF-related changes, or death	• Time to disease progression with progression being defined as ≥10% decline in FVC_{pp} from Baseline, IPF-related hospitalization, or death
• To assess the development of ADA against MTX-463	• Presence, titer, and impact of ADA
• To assess the effect of MTX-463 on biomarkers of IPF	• Change from Baseline to Week 24 in the PROLIFIC panel of 12 biomarkers (matrix metalloproteinase-7 [MMP-7], surfactant protein D [SP-D], Krebs von den Lungen-6 [KL-6], plasminogen activator inhibitor 1 [PAI-1], cancer antigen 19-9 [CA-19-9], cytokeratin 19 fragment [CYFRA 21-1], chemokine ligand 13 [CXCL13], soluble intercellular adhesion molecule 1 [sICAM1], chemokine ligand 18 [CCL18], periostin (POSTN), cancer antigen 125 [CA-125], and tenascin C [TNC]) • Change from Baseline to Week 24 in tissue inhibitor of metalloproteinase-1 [TIMP-1], chemokine ligand 2 [CCL2], propeptide of type 3 collagen [Pro-C3], propeptide of type 6 collagen [Pro-C6], C7M, and interleukin-6 [IL-6]
• To assess the effect of MTX-463 on biomarkers of bone remodeling	• Change from Baseline to Week 24 on procollagen type I N-terminal propeptide [P1NP] and C-terminal cross-linked telopeptide of type 1 collagen [CTX]

6. STUDY DESIGN

6.1 Study Design/Type

This is a randomized, double-blind, placebo-controlled study designed to assess the safety and tolerability of MTX-463 in participants with IPF. The schematic diagram of the study design is presented in Figure 1.

Randomization will be stratified by concomitant use of approved therapy. Enrollment will be monitored during the study to ensure that approximately half of the participants will be on concomitant therapy; one subpopulation or the other could be held if an imbalance is appearing.

6.1.1 Data Safety Monitoring Board

The safety of ongoing participants in this study will be overseen by a data safety monitoring board (DSMB). The DSMB will consist of physicians independent of the study with expertise in lung disease as well as an independent statistician. Additional details of the composition of the DSMB and the frequency at which they will meet can be found in the DSMB charter.

6.2 Randomization

Approximately 164 participants with IPF who meet the study's inclusion and exclusion criteria will be randomly assigned in a 1:1 ratio to receive MTX-463 or a matching placebo.

Participants will be assigned to treatment via Interactive Response Technology. Assignment will be stratified according to concomitant use of nintedanib, pirfenidone, or nerandomilast at Baseline.

6.3 Blinding and Unblinding

The clinical study will be performed in a double-blind manner. All participants, site personnel (except the onsite pharmacist), and the Sponsor will be blinded to study drug assignment. The following controls will be employed to maintain the double-blind status of the study:

- The placebo IV infusions will be identical in appearance to the IV infusions with MTX-463.
- The Investigator and other staff members involved with the study will remain blinded to the treatment randomization code during the dose preparation procedure. All investigational product handling, preparation, dispensation, and receipt must be conducted exclusively by unblinded personnel (e.g., onsite pharmacist).

The study blind should not be broken except in a medical emergency (where knowledge of the study drug administered would affect the treatment of the emergency), as participant safety must always be the first consideration in making such a determination. The decision to break the blind will be made on a case-by-case basis, at the discretion of the Investigator in collaboration with the Medical Monitor. Treatment assignment of individual participants will be unblinded during the study if this information is required to manage a serious adverse event (SAE). The Pharmacy Manual provides details on the procedures for unblinding treatment assignment by investigators. The Investigator should contact the Medical Monitor prior to unblinding a participant's intervention assignment, unless this could delay emergency treatment for the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours of this occurrence. The date and reason for the unblinding must be recorded.

After database lock, the overall randomization code will be broken for reporting purposes.

6.3.1 Interim Analysis

The Sponsor will conduct an interim analysis (IA) after approximately 50% of the participants complete their 24-week visit or discontinue from the study. The IA will be conducted by a separate unblinded team. No one involved in the day-to-day oversight and management of the study can be unblinded at the IA. The IA will be for internal decision-making purposes.

6.4 Study Treatment(s)

Study treatment comprises administration of either the study drug MTX-463 or matched placebo.

MTX-463 is not approved for marketing in any region in the world.

Placebo control was selected to allow for a broad population of IPF participants to be studied, including those on current approved therapies.

6.5 Dose and Dosage Regimen of Investigational Product

Participants will receive either MTX-463 or a matching placebo by Q4W IV infusion(s).

The MTX-463 dosing comprises a CCI mg/kg loading dose on Day 0 (Week 0) followed by CCI mg/kg Q4W maintenance doses on Weeks 4, 8, 12, 16, and 20 (see Table 1).

6.6 Preparation, Handling, Storage, and Accountability of Investigational Product

6.6.1 Accountability Procedures for the Investigational Product

Treatment will be administered onsite by site personnel at the designated visits (see Table 1). Delayed, missing, or omitted doses will be considered a dosing noncompliance. Permanent discontinuation of study treatment should be discussed with the Sponsor and logged in the applicable eCRF.

The Investigator is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The Investigator (or designee) will maintain an accurate record of the study supplies received and in inventory. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each participant and the date of dispensing. Drug accountability records will be available for review and inspection at any time. The original drug accountability records will be available for review by the Sponsor upon request, and the drug accountability log will be retained as a part of study records at the completion of the study. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.6.2 Dosage Form, Packaging, and Labeling of Investigational Product

MTX-463 is a solution for IV infusion. MTX-463 will be packaged in glass vials. The Sponsor will supply MTX-463; the placebo will be procured by the site. Each vial will be labeled as required per applicable regulatory standards.

6.6.3 Product Handling and Storage

The long-term storage condition for MTX-463 drug product is 2°C to 8°C. Further details on product handling and storage can be found in the MTX-463 IB.

6.6.4 Preparation of Investigational Product

MTX-463 will be supplied as a liquid formulation for IV infusion. Further details on preparation of the drug product can be found in the Pharmacy Manual.

6.7 Duration of Participant Participation

The maximum duration of participation for an individual in the study is expected to be 32 weeks, which includes a 4-week Screening Period, a 24-week Treatment Period (including End-of-Treatment visit), and a 4-week Safety Follow-Up Period.

No post-study access to MTX-463 is planned for participants.

6.8 Sequence and Duration of Trial Periods

The study start date is defined as the date of the first written informed consent.

The study completion date is defined as the last participant last visit (LPLV) (at End of Study [EOS]).

6.8.1 Screening Period

The Screening procedures to determine participant eligibility will be performed within 28 days before the start of the study drug. The Screening evaluations will occur for the specified assessments as described in the Schedule of Assessments (SoA) (Table 1). Following completion of all Screening assessments, eligibility documentation must be submitted for evaluation and approval by the Medical Monitor prior to randomization.

Rescreening may be permitted in certain cases, if approved by the Medical Monitor.

Participants will be randomly assigned in a 1:1 ratio any time from Day -2 to Day 0 to receive either MTX-463 or placebo starting on Day 0.

6.8.2 Baseline, Treatment, and Follow-Up

Pre-dose evaluations will occur at Baseline (Week 0 on Day 0) and within 2 hours prior to study drug administration, when possible, for specified timepoints as detailed in the SoA (Table 1).

Participants will receive IV infusions of the study drug administered over 75 minutes (±15 minutes) for the loading dose level and over 60 minutes (±15 minutes) for the maintenance (Q4W) dose level per the procedure outlined in the Pharmacy Manual; they will return to the site for their remaining study drug doses and follow-up assessments. Each participant will undergo assessments at specified timepoints at Week 0 (Day 0) through Week 28 (Day 196) as detailed in Section 3.3. End-of-Treatment (EOT) procedures will be completed at Week 24 (Day 168) or upon early termination (ET). An EOS assessment will be completed at Week 28 (Day 196).

6.9 Discontinuation Criteria

6.9.1 Participant Withdrawal From the Study

A participant may withdraw from the study at any time for any reason. Participants may choose to withdraw from study treatment but agree to remain on study for follow-up contact; this must be recorded by the study site. If a participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

A participant may also be withdrawn from the study at the discretion of the Investigator at any time for safety, behavioral, or compliance reasons.

In the event of a participant withdrawal, the Sponsor should be notified of the date and reason for the participant's withdrawal from the study.

If a participant is withdrawn from study, all efforts should be made to complete an EOT visit as well as an EOS visit, as shown in the SoA (Table 1). Other procedures may be performed at the Investigator's (or designee's) and/or Sponsor's discretion. The participant will be permanently discontinued from study intervention and the study at that time. All AEs and SAEs should be monitored and reported as detailed in Section 9.2.

6.9.2 Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the site for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, they will be considered to be lost to follow-up and discontinued from the study.

6.9.3 Rescue Therapy

A participant who meets the criteria for IPF progression, either because they have experienced a ≥10% decline in FVC_{pp} from Baseline, or because they have been hospitalized due to IPF, may be permitted to withdraw from treatment with study drug and instead receive rescue therapy with any approved agent for IPF. Participants will continue to be followed for safety. The Medical Monitor should be contacted prior to stopping study drug treatment or beginning rescue medication.

6.10 Stopping Criteria

Unless participant safety precludes doing so, the Medical Monitor should be consulted prior to stopping dosing of study drug in an individual participant.

Discontinuation of study drug administration does not necessarily mean discontinuation from the study. Participants who discontinue treatment with study drug should be asked to continue in the study to be followed for safety and to complete all remaining study procedures as indicated by this protocol. Any new clinical finding is to be reported as an AE.

6.10.1 Study-Drug Stopping Rules for Individual Participants

Study drug administration must be stopped, and the Medical Monitor notified, if any of the following events occur:

- A participant becomes pregnant.
- A participant demonstrates significant or repeated non-compliance with the protocol (e.g., use of prohibited medications, repeated failure to attend study visits), which, in the opinion of the Investigator and in consultation with the Sponsor, may compromise participant safety, study drug evaluation, or data integrity.
- A participant develops a serious or severe AE that is deemed related to study drug, and the Investigator determines that it is no longer in the best interests of that participant to continue.
- A participant is deemed to have experienced treatment failure, defined as progression of their IPF, and the Investigator determines that it is no longer in the best interests of that participant to continue.
- Any other condition occurs that, in the opinion of the Investigator, significantly jeopardizes the wellbeing and safety of the participant(s), and that prevents the participant(s) from continuing with the study.

6.10.2 Study Stopping Criteria

The DSMB will have the authority to recommend the study be stopped if they determine that continuing the study poses an undue risk to the safety of the ongoing participants.

In the event of a negative change in risk/benefit assessment or relevant toxicity, including an unexpected drug-related SAE, severe TRAE, or TRAE leading to death, treatment will be held in all participants pending evaluation by the Sponsor and DSMB recommendation.

The study may be prematurely terminated by the Sponsor. Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Medical or ethical reasons affecting the continued performance of the study.
- Difficulties in the recruitment of participants.
- Insufficient adherence to protocol requirements.
- Plans to modify, suspend, or discontinue study drug development.

6.11 Data Handling and Record Keeping

All participant data relating to the study will be recorded on electronic case report forms (eCRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. Study monitors will perform ongoing source-data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the International Council on Harmonisation (ICH), Good Clinical Practice (GCP), and all applicable regulatory requirements.

6.11.1 Monitoring and Direct Access to Source Data and Documents

Clinical research associates (CRAs) representing the Sponsor will routinely visit the study site throughout the study. The Investigator will also ensure that the monitor, or other compliance or quality assurance reviewer, is given access to all study-related documents and study-related facilities (e.g., pharmacy, diagnostic laboratory, medical records), and has adequate space to conduct the monitoring visit. In addition to the monitoring visits, frequent communication (email, letter, telephone, and/or fax) by the CRA will ensure that the investigation is conducted according to protocol design and regulatory requirements. The Investigator, or appropriate designee, will allocate adequate time for monitoring activities and follow-up correspondence.

The CRA will review ICFs, eCRFs, and laboratory and other diagnostic reports, comparing them with source documents to verify adherence to the protocol and to ensure complete, accurate, consistent, and timely collection of data. The CRA will record and report any protocol deviations not previously sent to the Sponsor. The CRA will confirm that AEs and SAEs have been appropriately documented and reported in accordance with regulatory requirements. They will also confirm that all SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC. The Investigator will be asked to provide any missing information or to clarify any discrepancies found by the CRA/monitor. It is expected that the Investigator will be present for a concluding review at the end of each monitoring visit.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigational site.

The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, AE and concomitant medication reporting, and raw data collection forms) designed to record all observations and other pertinent data for each participant. The Investigator, their designees, and site study monitors have direct access to source data and documents for the purposes stated above in Section 6.11.

The Investigator must permit study-related monitoring, audits, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) reviews, and regulatory agency inspections and must provide direct access to source-data documents to those entities for those purposes.

6.11.2 Study Record Retention

Records and documents, including signed informed consent forms (ICFs), pertaining to the conduct of this study must be retained by the Investigator until final marketing authorization approval after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

7. SELECTION OF PARTICIPANTS

To be eligible for this study, participants must meet all of the inclusion criteria and none of the exclusion criteria. In the event of a screen failure, a one-time rescreen may be permitted for participants in this study. Any rescreening attempts must be evaluated and approved by the Medical Monitor.

7.1 Criteria for Inclusion

1. Participants with IPF of any gender ≥40 years of age at time of signing the informed consent
2. Able to understand the study and provide signed, written informed consent
3. Able to read and understand the language of the informed consent and other study-related materials
4. Meet the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (ALAT) 2019 criteria for the diagnosis of IPF[1]; diagnosed with IPF within 7 years of Screening
5. If a participant is on treatment with pirfenidone, nintedanib, or nerandomilast, the dose of these medications must be stable for ≥90 days prior to Screening with plans to maintain the same dose throughout the study Treatment Period. Use of any of these 3 agents in combination with each other is not permitted.
6. If a participant was on treatment with nintedanib, pirfenidone, or nerandomilast, and the agent has been discontinued; this must have occurred ≥30 days prior to Screening. At Screening, there must also be no plan to start any of these medications for the duration of the study. Participants newly diagnosed with IPF who, in the judgment of the treating physician, are considered in need of treatment with nintedanib, pirfenidone, or nerandomilast, should not defer standard of care treatment and should be excluded from the study.
7. FVC of ≥45 percent predicted (pp) at Screening
8. DLCO of ≥25 pp at Screening
9. Willing and able to complete all protocol-required study visits and procedures
10. Female participants of childbearing potential have a negative serum pregnancy test at Screening and must agree to use and follow medically approved, highly effective methods of contraception during treatment and until 5 half-lives or 125 days after the last dose of study drug, whichever is longer (see Appendix 3 for details).
11. Male participants with female partners of childbearing potential must use condoms during the treatment and until 5 half-lives or 125 days after the last dose of study drug, whichever is longer (see Appendix 3 for details).

7.2 Criteria for Exclusion

1. Acute exacerbation of IPF within 6 months of Screening or during the Screening Period
2. Forced expiratory volume in 1 second (FEV1)/FVC ratio of < 0.7 at Screening

3. Requirement for continuous supplemental oxygen. Intermittent supplemental oxygen use (e.g., during exercise or sleep) is permitted
4. Expected to receive a lung transplant within the study duration
5. Current active bacterial infection or use of antibiotics for suspected lung infection in the 30 days prior to Screening
6. Planned surgery within the study duration
7. Clinically significant pulmonary hypertension
8. Use of immunosuppressive therapy (excluding corticosteroids). If previously on such agents, they should have been discontinued for at least 5 half-lives or 90 days, whichever is longer, prior to Screening.
9. Use of systemic corticosteroids (prednisone or equivalent) at a dose of >10 mg once daily within 30 days prior to Screening
10. Currently smoking or vaping
11. Current known malignancy, or history of cancer, or lymphoproliferative disorder other than non-melanomatous skin cancers, within 2 years of Screening
12. Current infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV)
13. Currently pregnant, breast feeding, or planning to conceive for the length of the study
14. History of severe depression, psychosis, or suicidal ideation, as determined by the Investigator, within 2 years of Screening
15. Any clinically significant disease or laboratory abnormality detected at Screening that might interfere with a participant's ability to complete the study, on-study evaluations, or participant safety
16. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2× upper limit of normal (ULN) at Screening
17. Presence of interstitial lung disease due to any cause other than IPF, clinically significant cardiovascular disease, or any other concurrent active medical condition determined by the Investigator to interfere with the participant's ability to complete the study
18. Known allergy to MTX-463 or any of its excipients, or a history of a prior allergic reaction to a monoclonal antibody therapeutic
19. Any prior use of MTX-463 or other therapy targeting WISP1
20. Any other concurrent experimental agent or an active part of any other clinical study, unless they have stopped taking the investigational product at least 5 half-lives or 30 days before Screening, whichever is longer

8. TREATMENT OF PARTICIPANTS

8.1 Treatment to Be Administered

Arm Name	MTX-463	Placebo
Intervention Name	MTX-463	Placebo
Dose Formulation	Injectable solution	Injectable solution
Unit Dose Strength(s)	CCI mg/mL	Matching placebo
Dosage Level(s)	CCI mg/kg loading dose followed by CCI mg/kg maintenance doses	Matching placebo
Dosage regimen	MTX-463 loading dose, followed by 5 maintenance infusions Q4W	Matching placebo for 6 infusions Q4W
Route of Administration	Intravenous infusion	Intravenous infusion
Use	Experimental	Placebo
Investigational medicinal product (IMP) and Noninvestigational medicinal product (NIMP)	IMP	IMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the sites based on regional availability

8.2 Medications and Procedures Permitted and Not Permitted

Prior medications and procedures are those administered or performed within 28 days of the first dose of study drug. Any prior use of pirfenidone, nintedanib, or nerandomilast is considered a prior medication. Concomitant medications and procedures are those administered or performed from the first dose of study drug until the participant's final visit.

Concomitant medications permitted during the study will include pirfenidone, nintedanib, and nerandomilast for those who enter the study on one of these medications at a stable dose (see Section 7.1), and medications to treat concurrent medical issues such as diabetes or hypertension.

Otherwise, concomitant medications and procedures will be allowed only for the treatment of AEs as deemed medically necessary.

9. STUDY ASSESSMENTS AND PROCEDURES

Planned timepoints for all study assessments are provided in the SoAs (Section 3.3).

Every effort will be made to schedule and perform the procedures as closely as possible to the planned timepoint outlined in the SoA, considering appropriate conditions, practical restrictions, and the other procedures to be performed at the same timepoint. Actual times are to be recorded in the eCRF.

Collected biological samples will be used only for protocol-specified analyses. Once the clinical study report (CSR) is final, samples will be destroyed in accordance with applicable regulations and site-specific procedures. No samples are intended to be retained for future use beyond the scope of the study.

9.1 Efficacy Assessments

9.1.1 Spirometry

Spirometry assessments will be conducted per the timepoints in the SoA (Table 1) and include FEV1 and FVC.

Spirometry assessments will be conducted to evaluate pulmonary function and will be administered by a trained, certified, and qualified healthcare professional (e.g., physician, physician assistant, nurse practitioner, nurse, medical technician). In addition to appropriate professional qualifications, all individuals administering spirometry in this study must be trained and certified by the study-designated vendor. Only those certified by the vendor will be permitted to perform the assessments. Standardized spirometry equipment will be provided for each site and must be used for all assessments to ensure consistency across study locations. Bronchodilator use (short- and long-acting) will not be permitted on the day of spirometry prior to the assessment.

When possible, the same healthcare professional should perform the assessments for a given participant throughout the study to ensure consistency. To minimize variability, whenever possible, spirometry should be conducted at approximately the same time of day for each scheduled assessment. Each site will perform at least 1spirometry series (8 efforts) and transmit test results to the vendor for human overread. A maximum of 3 spirometry series of up to 8 efforts each will be allowed on a single visit. All spirometry tests will be centrally reviewed to ensure they meet acceptability criteria. The site can repeat spirometry any number of times deemed acceptable and reasonable to the Investigator during the Screening period, using direct feedback from human overreads.

Detailed instructions on the conduct of spirometry, including calibration, technique, and data recording, will be provided in the study-specific manual, which should be referenced for specific guidance on conducting assessments in accordance with study requirements.

9.1.2 Diffusing Capacity of the Lungs for Carbon Monoxide

The DLCO assessment will be performed to evaluate the lungs' ability to transfer carbon monoxide (CO) across the alveolar-capillary membrane. Each site should utilize its own equipment to perform this test, adhering to the 2017 ERS/ATS standards for single-breath carbon monoxide uptake. Please refer to these guidelines for detailed technical specifications and procedural requirements[13].

The test should be conducted by a trained healthcare professional with experience in pulmonary function testing. To ensure consistency, personnel responsible for performing DLCO assessments should be familiar with and trained in the standardized procedures outlined in the 2017 ERS/ATS guidelines.

DLCO will be performed at applicable timepoints after spirometry as described above. To prevent nasal breathing, participants should wear a nose clip and use a well-fitted mouthpiece. To reduce variability, participants should avoid exposure to carbon monoxide (e.g., pollution or second-hand smoke) before testing. Please refer to the 2017 ERS/ATS guidelines for additional pre-testing restrictions.

During the test, participants will first exhale fully to residual volume (RV). They will then take a deep, rapid breath, ensuring they inhale at least 85% of the test gas volume within 4 seconds until they reach total lung capacity (TLC). This is followed by a breath-hold for 10 seconds, with an acceptable range of ±2 seconds, during which the participant should remain still to ensure accuracy. Following the breath-hold, participants will exhale in a controlled manner. Specific requirements on breathing technique, gas composition, and volume measurement can be found in the 2017 ERS/ATS guidelines.

For reliable test results, a minimum of 2 acceptable test maneuvers must be obtained, ensuring that the 2 highest values fall within the acceptable repeatability range (within 2.0 mL/min/mmHg [0.67 mmol/min/kPa] of each other). If this repeatability threshold is not met, additional maneuvers should be performed, with a maximum of 5 attempts per participant. If a participant is unable to produce 2 repeatable values within the allowed attempts, the test should be documented as non-reproducible and documented as a screen failure. Please refer to the 2017 ERS/ATS guidelines for exact repeatability criteria.

All DLCO testing equipment should meet the performance standards specified in the 2017 ERS/ATS guidelines, including requirements for volume accuracy, gas analyzer response time, and calibration. Regular calibration and quality control checks must be performed per manufacturer recommendations and guideline standards to ensure accurate and reproducible measurements.

To minimize variability, the same healthcare professional should conduct DLCO assessments for each participant whenever possible. Additionally, testing should be scheduled at the same time of day for each visit when feasible. These steps help maintain consistency across study sites and improve data reliability.

9.1.3 High-Resolution Computed Tomography Scan

A high-resolution computed tomography (HRCT) scan of the chest will be obtained at Screening if needed to confirm the diagnosis (Table 1). Since the HRCT scans will be performed using site-specific equipment and protocols, the actual radiation dose may vary; however, the approximate radiation exposure level will be 4 mSv for this study. An HRCT scan performed in the 90 days prior to Screening that supports the diagnosis of IPF or a lung biopsy diagnostic of IPF can be used in lieu of performing an HRCT during Screening. All HRCTs, including those performed prior to Screening, will be centrally read and confirmed to meet the diagnostic criteria for IPF by the central reader.

9.1.4 Living with Pulmonary Fibrosis Questionnaire

The L-PF Questionnaire was developed to assess quality of life in participants with fibrosing interstitial lung diseases[14].

The questionnaire consists of 44 items divided into two modules: Symptoms (23 items) and Impacts (21 items). The Symptoms module assesses shortness of breath, cough, and fatigue in the past 24 hours. For each of the shortness of breath items, respondents are asked to rate shortness of breath resulting from doing activities of varying intensities that span a range of metabolic demands. Because some respondents may not perform certain activities, each item first asks whether the respondent performed the activity in the last 24 hours; if they did, they proceed to rating their shortness of breath; if they did not perform the activity in the last 24 hours, they are asked whether they did not have the opportunity to do it (e.g., a respondent who does not have stairs in their home may not have had the opportunity to climb a flight of stairs in the last 24 hours) or whether they avoided the activity because it was too difficult to perform. The Impacts module assesses multiple aspects of health-related quality of life (QOL) with a recall period of 1 week. Items in both modules have response options on a 5-option numeric rating score with an anchor of 0 “Not at all” to 4 “Extremely.” Overall scores range from 0 to 100, with higher numbers indicating a greater impairment.

9.1.5 WISP1 Levels and Biomarkers of Fibrosis

Serum samples for analysis of CCI of WISP1, TIMP-1, CCL2, Pro-C3, Pro-C6, C7M, IL-6; the PROLIFIC panel of 12 biomarkers (MMP-7, SP-D, KL-6, PAI-1, CA-19-9, CYFRA 21-1, CXCL13, sICAM1, CCL18, POSTN, CA-125, and TNC); and bone remodeling biomarkers P1NP and CTX will be collected during the study at the timepoints depicted in the SoA (Section 3.3).

Serum samples will not be retained once the CSR is final; see Section 9.

9.2 Safety Assessments

9.2.1 Physical Examinations

A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. A full physical examination will be completed at Screening and Day 0 and will be symptom-directed at each subsequent visit.

9.2.2 Vital Signs

Temperature, heart rate, respiratory rate, blood pressure, and pulse oximetry will be assessed. Vital sign measurements may be repeated at the discretion of the Investigator.

Blood pressure and heart rate should be assessed while the participant is supine. Blood pressure and heart rate should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

9.2.3 Body Weight

Body weight (preferably in light clothing or a gown and without shoes) will be measured at Screening, Baseline, and Week 28 (calibrated when possible).

9.2.4 Height

Height should be measured without shoes using a consistent device for all participants. Height will be measured at Screening and will be used to calculate body mass index (BMI).

9.2.5 Clinical Laboratory Tests

Laboratory tests should be collected after vital signs measurements, when applicable.

Hematology

Hematology laboratory tests will include hematocrit, red blood cell (RBC) count, hemoglobin, and platelet count. The RBC indices will include mean corpuscular volume, mean corpuscular hemoglobin, and % reticulocytes; white blood cell count with differential (absolute and percentage) neutrophils, lymphocytes, monocytes, eosinophils, and basophils.

Chemistry

Chemistry laboratory tests will include blood uric acid, creatinine, aspartate aminotransferase /serum glutamic-oxaloacetic transaminase, alanine aminotransferase/serum glutamic-pyruvic transaminase, gamma-glutamyl transferase, alkaline phosphatase, total and direct bilirubin, creatine kinase, total protein, albumin, glucose (random), potassium, sodium, chloride, calcium, magnesium, phosphorus, amylase, and lipase.

Other

Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and anti-hepatitis C virus [HCV]) will be performed.

The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If clinically significant values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
- All protocol-required laboratory tests must be conducted in accordance with the Laboratory Manual and the SoA (Section 3.3).
- If supplementary laboratory tests are required, any clinically significant results as determined by the Investigator (e.g., SAE, AE) must be recorded.

9.2.6 Concomitant Medications and Procedures

At each study visit, participants will be asked about what medications they are taking (started/stopped or adjusted dose). If the participant must use concomitant medication or concomitant procedures during the study, it is the responsibility of the Investigator to ensure that details regarding the medication or procedures are recorded on the eCRF.

A reasonable effort is to be made to document any medications or procedures the participant receives from the date that the ICF is signed until Week 28 (EOS).

The concomitant medication names will be coded by the Sponsor according to the World Health Organization Drug Dictionary (WHO-DD) and classified by anatomical therapeutic chemical categories.

9.2.7 Adverse Event and Serious Adverse Event Definitions

The definitions of AEs and SAEs are described below. The methods of recording, evaluating the severity, and assessing the causality of AEs and SAEs, as well as the required procedures for completing and transmitting SAE reports, are described in the ensuing sections.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE, and they remain responsible for following up on all AEs and SAEs considered related to the study intervention or study procedures, or that caused the participant to discontinue the study treatment. Participants are also encouraged to report AEs occurring at any other time during the study.

An AE is defined as any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

The events that meet the AE definition include:

- Any abnormal laboratory test results (hematology or clinical chemistry) or other safety assessments (e.g., radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in frequency or intensity of the condition or both
- New conditions detected or diagnosed after study intervention administration, even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

The events that DO NOT meet the AE definition include:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments associated with an underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy, tooth extraction), if the condition that leads to the procedure is the AE
- Routine, scheduled medical or surgical procedures (e.g., colonoscopy, dental cleaning)

- Situations in which an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent disability/incapacity
- Results in a congenital anomaly/birth defect

The Investigator must report all SAEs to the Sponsor immediately, and no later than 24 hours after becoming aware of the event. In addition, the Investigator is responsible for reporting SAEs to the IRB/IEC in accordance with applicable regulations and the requirements of the IRB/IEC.

9.2.8 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

9.2.8.1 Method of Recording AEs and SAEs

The method of recording AEs and SAEs and the procedures for completing and transmitting SAE reports are described below:

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor (or designee) in lieu of completion of the AE/SAE eCRF pages.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor (or designee). In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor (or designee).
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Care will be taken not to introduce bias when detecting AEs or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences. Participants will also be encouraged to spontaneously report AEs occurring at any other time during the study.

9.2.8.2 Reporting and Timing of Safety Parameters

All SAEs will be collected from the signing of the ICF through the last study visit, and all AEs will be collected from the first dose of study drug administration through the last study visit. All AEs and SAEs will be assigned a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade (1-5) (Section 9.2.8.4). Medical occurrences that begin before signing of the ICF will be recorded in the Medical History/Current Medical Conditions section of the eCRF, not in the AE section. Any worsening of a medical occurrence after signing of the ICF is to be reported as an SAE (if criteria are met) or as an AE after the first dose.

All SAEs will be recorded and reported to the Sponsor or designee immediately, and under no circumstance should this exceed 24 hours. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

9.2.8.2.1 Treatment and Notification of Overdose

Overdose is not a concern for this study as dosing will be administered at the study site by the Investigator or their qualified designee. Additionally, MTX-463 has been investigated at doses up to 30 mg/kg, which was well tolerated with no reported safety concerns.

Deviations in dosing administration will be reported as a protocol deviation.

9.2.8.3 Regulatory Reporting Requirements for SAEs and SUSARs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other relevant regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

For all studies, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and must be forwarded to Investigators as necessary. A SUSAR is defined as an adverse reaction to an investigational medicinal product that is both serious and unexpected, and for which a causal relationship with the investigational medicinal product is considered at least reasonably possible. A serious adverse reaction (SAR) is an adverse reaction that meets the criteria for seriousness (e.g., results in death, is life-threatening, requires hospitalization or prolongation of hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect). The nature, severity, or outcome of a SUSAR is not consistent with the reference safety information. The Sponsor or designee will be responsible for notifying the relevant regulatory authorities of any SUSAR and reporting it to the Eudravigilance database, as outlined in Article 42 of Regulation (EU) No. 536/2014. When reporting a SUSAR to the

Agency, the Sponsor shall only unblind the treatment allocation of the affected participant to whom the SUSAR relates (Annex III, paragraph 18 of CTR 536/2014).

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review it and file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

9.2.8.4 Assessing the Severity and Causality of Events

Adverse events will be graded using the NCI CTCAE, version 6.0. The severity of AEs will be coded and graded on a scale of 1 (mild) to 5 (death related to AE), per CTCAE guidelines.

The 5-level grading scale for the CTCAE system includes specific descriptions for each grade:

- Grade 1: Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate, minimal, local, or noninvasive intervention indicated; limiting instrumental activities of daily living (ADL) or mild/moderate impact on age-appropriate normal daily activity
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL or severe impact on age-appropriate normal daily activity
- Grade 4: Life-threatening consequences, urgent intervention indicated
- Grade 5: Death related to the AE

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator must document their assessment of causality.

- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, not merely that a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship. The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data.
- The Investigator will also consult the IB in their assessment.

9.2.9 Type and Duration of Participant Follow-Up After Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 6.9.2). Further information on follow-up procedures is provided below:

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor (or designee) to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor (or designee) with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed eCRF.

9.2.10 Collection of Pregnancy and Postpartum Information

Participants of childbearing potential must agree to use and follow medically approved, highly effective methods of contraception during treatment and until 5 half-lives or 125 days after the last dose of study drug, whichever is longer. If a pregnancy is reported in a study participant, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined below. For participants with partners who become pregnant, after obtaining the necessary signed informed consent from the pregnant partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy.

Participants who become pregnant or participants with partners who become pregnant will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Follow-up should not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs. A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at ≥22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 9.2.8.2. Although the Investigator is not obligated to actively seek this information in former study participants, they may learn of an SAE through spontaneous reporting.

9.3 Pharmacokinetic Assessments

Serum concentrations of MTX-463 will be determined using a validated analytical procedure. Summary statistics for all PK concentrations by timepoint, dose, and study day will be provided.

Sparse PK serum samples will be collected at timepoints as depicted in the PK SoA (Table 2). The concentration data from this study will be used to explore any relationship between MTX-463 exposure and clinical response, PD endpoints, AEs, and covariates, as data permit. These data will be analyzed together with PK data from other clinical studies for population PK analyses, as appropriate.

Serum samples will not be retained once the CSR is final; see Section 9.

9.4 ADA Assessments

Serum samples for analysis of ADA will be collected pre-dose at Weeks 0, 4, and 12 (on Days 0, 28, and 84), Week 20 (Day 140), Week 24 (Day 168), and Week 28 (Day 196) (Table 1) and analyzed using validated procedures. Samples will be screened for ADA positivity, with positive screens undergoing additional testing for the extent of signal inhibition in a confirmatory assay, and titering.

Serum samples will not be retained once the CSR is final; see Section 9.

10. STATISTICS

10.1 Participants to Be Included in the Analyses

The Safety Analysis Set will consist of all participants who received at least one dose of study drug (MTX-463 or placebo). This analysis set will be used for all safety analyses.

The Efficacy Analysis Set will consist of all participants who received at least one dose of study drug and had at least one post-treatment FVC assessment.

The PK Analysis Set will consist of participants who have received at least one dose of MTX-463 or placebo, and who have measurable serum concentration data. This analysis set will eventually be used in subsequent population PK analyses.

10.2 Statistical Methods

The Statistical Analysis Plan (SAP) will specify the details of the planned statistical analyses, as well as the statistical methods and display formats that will be used for summarizing and reporting the study results. Intercurrent events and their handling strategies will be detailed in the SAP. Tables and listings will present results by treatment and will include demographic information, disposition, medical history, and concomitant medications. Safety and efficacy parameters will be derived and presented. Protocol deviations will be listed.

The details of the planned statistical analyses for key assessment parameters are described below.

10.2.1 Sample Size

A sample size of approximately 164 participants, with approximately 82 participants per treatment arm, was selected based on the following assumptions:

CCI [redacted]
CCI [redacted]
CCI [redacted]
CCI [redacted]

- Expected dropout rate of 10%
- 2-sided alpha level of 0.05 and 80% power

10.2.2 Forced Vital Capacity Analyses

Changes from Baseline in FVC will be estimated using a mixed-effect model for repeated measures (MMRM) analysis. The model will include fixed effects for treatment, scheduled visit, treatment-by-visit interactions, and concomitant nintedanib, pirfenidone, or nerandomilast (yes/no) as categorical variables, along with Baseline FVC and Baseline FVC-by-visit interaction as continuous covariates. Missing data will be handled implicitly within the MMRM model, based on the assumption that data are missing at random. Data from participants who initiate rescue therapy will be censored at the time of first use. However, data from participants who discontinue the study drug but do not subsequently receive rescue therapy will remain included in the analysis. Sensitivity analyses for handling missing data will be detailed in the SAP.

Changes from Baseline in FVC_{pp} will be estimated using the same model used for the primary efficacy model.

For participants with and without concomitant nintedanib, pirfenidone, or nerandomilast, change from Baseline in FVC will be estimated separately using a mixed-effect model similar to the primary efficacy analysis model

10.2.3 Diffusing Capacity of the Lungs for Carbon Monoxide

Changes in DLCO across time will be estimated using descriptive statistics. ANCOVA will be used to adjust for Baseline.

10.2.4 Safety Analyses

All safety results will be summarized using descriptive statistics for the placebo control and MTX-463 arms studied using the Safety Analysis Set. All AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA) terms.

TEAEs are defined as AEs with onset after administration of the first dose of study treatment or preexisting conditions that worsen after administration of the first dose of study treatment. TEAEs, TRAEs, TEAEs by maximum severity, and serious TEAEs will be summarized. Listings will be provided of all AEs, serious TEAEs, fatal TEAEs, and TEAEs leading to discontinuation.

Descriptive statistics for vital signs, physical examination, and clinical laboratory parameters, including change from Baseline when applicable, will be summarized by timepoint. The incidence of clinically significant changes in selected laboratory parameters also will be summarized.

10.2.5 Pharmacokinetic Analyses

Serum concentrations for MTX-463 will be listed and summarized using descriptive statistics.

Sparse PK samples will be used to explore any relationships between MTX-463 exposure and clinical response, pharmacodynamic (PD) endpoints, AEs, and covariates, as data permit. These data will be analyzed together with PK data from other clinical studies for population PK analyses, as appropriate.

10.2.6 ADA Analyses

The incidence and prevalence of ADA in the treated groups will be assessed. The time to ADA development, as well as the association between ADA presence and safety, efficacy, and PK concentrations, will also be explored, as feasible.

10.2.7 Living with Pulmonary Fibrosis Questionnaire

Assessments of L-PF Questionnaire scores[14] will be conducted at the timepoints given in the SoA (Table 1).

Participants will complete the L-PF for Symptoms domain and for Impacts domain. The L-PF Questionnaire will be evaluated at Weeks 0 and 24 (Baseline and Day 168).

Change from Baseline in L-PF scores will be estimated in the treatment groups using analysis of variance techniques.

10.2.8 WISP1 Level Assessment and Biomarkers of Fibrosis

Descriptive summaries statistics by timepoint will be used to describe the following:

CCI [redacted]

CCI [redacted]

CCI [redacted]

- Change from Baseline in TIMP-1, CCL2, Pro-C3, Pro-C6, C7M, and IL-6 levels
- Change from Baseline in the PROLIFIC panel of 12 biomarkers (MMP-7, SP-D, KL-6, PAI-1, CA-19-9, CYFRA 21-1, CXCL13, sICAM1, CCL18, POSTN, CA-125, and TNC)
- Change from Baseline in bone remodeling biomarkers P1NP and CTX

10.2.9 Time to Disease Progression

Time to disease progression will be evaluated throughout the study and will be estimated using the Kaplan-Meier method.

Progression is defined as:

- ≥10% decline in FVC_{pp} from Baseline
- IPF-related hospitalization
- Death

10.3 Procedure for Missing, Unused, and Spurious Data

A detailed plan for dealing with missing data will be provided in the SAP.

10.4 Procedure for Reporting Deviations From the Original Statistical Plan

Any major deviations from the planned analyses will be detailed in the CSR.

10.5 Interim Analysis

The IA will evaluate change from Baseline to Week 24 in FVC, PK, and target engagement of MTX-463, as well as safety and other measures of efficacy. Descriptive statistics will be used to summarize the change from Baseline in FVC in each study arm.

11. QUALITY ASSURANCE AND QUALITY CONTROL

For quality assurance and consistent study data, procedures will be carried out only by the Investigator or trained staff under the direction of the Investigator. Study-related procedures will be carried out in accordance with the written materials (e.g., study manual, eCRF completion guidelines).

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor or a Sponsor's designee may conduct a quality assurance audit of the study center(s).

12. PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures, and the data to be collected on study participants. Additional assessments required to ensure the safety of participants should be administered as deemed necessary on a case-by-case basis. Under no circumstances is the Investigator allowed to collect additional data or conduct any additional procedures for any research-related purpose involving any investigational drugs under the protocol. Investigators ascertain they will apply due diligence to avoid protocol deviations. If the Investigator feels a protocol deviation would improve the conduct of the study, this must be considered a protocol amendment; and unless such an amendment is agreed upon by the Sponsor and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13. ETHICS DESCRIPTION AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH GCP Guidelines
- Applicable laws and regulations, including those pertaining to safety reporting and the collection and processing of personal data

The protocol, ICF, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be reviewed and approved by the IRB/IEC before the study is initiated.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. Protocol amendments will be prepared and approved by the Sponsor or Sponsor's designee and sent to the appropriate IRB/IEC for review and approval. Documentation of IRB/IEC approval must be forwarded to the Sponsor or designee before the procedures associated with the amendment commence.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor will provide this information to the Investigator.

13.1 Participant Information and Informed Consent

The Investigator will ensure that each participant is provided full and adequate information describing the nature, purpose, and possible risks and benefits of participating in the study; that each participant has time to consider the information; and that each participant has the opportunity to ask questions. Participants must be informed that participation in the study is voluntary and that they may discontinue at any time.

A signed and dated form documenting informed consent, as defined per local requirements, must be obtained from each participant before they participate in the study (i.e., before study-related procedures are conducted). The Investigator must maintain the original, signed and dated informed consent form, and a copy must be provided to the participant.

13.2 Data Protection

The participant must be informed that their personal study-related data will be used by the Sponsor in accordance with local data-protection law. The level of disclosure must be explained to the participant prior to providing their informed consent for the use of their data. Additionally, the participant must be informed that their medical records may be examined by authorized personnel appointed by the Sponsor, appropriate IRB/IEC members, and/or regulatory authorities.

Participants will be assigned a unique identifier by the Sponsor, which will be used on the eCRF or other documents submitted to the Sponsor. Participant names or other information that would make the participant identifiable will not be entered in the eCRF or database or transferred in other documents submitted to Sponsor.

The Investigator is responsible for ensuring that the source data are accurate, legible, and attributable. Computerized systems (and/or any other kind of electronic devices) used to create, modify, maintain, archive, retrieve, or transmit electronically any source data must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures.

The Sponsor, as the Data Controller, is responsible for ensuring that all processing activities involving personal data performed in the scope of this study are compliant with requirements including, but not limited to, those set by EU General Data Protection Regulation (GDPR 679/2016), its subsequent amendments, and any additional national laws on data-protection, recommendations, and guidelines as applicable. The data-protection responsibilities of the Sponsor and the clinical site are included in the site-specific contract, which will describe the handling of data security breaches, including mitigation measures, respective communication, and cooperation of the parties. Confidentiality of participants' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and national data-protection laws.

The Sponsor (Mediar Therapeutics, Inc.) has put in place a functional process of reporting of any data breach occurring at the Sponsor's or its subcontractor's facilities and premises.

In the event of any data breach, the Sponsor will immediately apply relevant measures to mitigate the risks to participants' data as appropriate in relation to the specific context of the data breach, taking into account factors such as its source, underlying intentions, and possibilities of recovery. These measures include, but are not limited to:

- Restriction and monitoring of physical access to the offices and information processing facilities to employees, personnel, and approved visitors
- Ensuring appropriate and restricted user access is relevant to the function and type of activity performed
- Implementing the pseudonymisation and encryption of personal data, as appropriate
- Implementing network, application, and database security by means of firewalls and antivirus/anti-malware
- Implementing procedures that cover documentation, reporting, analysis, monitoring, and resolution of security incidents
- Logging of security events/incidents in information systems
- Ensuring backup of information systems, computers, and software involved in the performance of the services provided in the study
- Developing and applying means to restore availability and access to personal information in a timely manner in the event of a security incident

Any data breach presenting material risks to the rights and freedoms of data participants will be reported to the relevant supervisory data-protection authority within 72 hours of the Sponsor becoming aware of the data breach. In addition, in case of a high-risk breach, data participants will be informed by the Sponsor, via the clinical study site.

13.3 Indemnification

The site-specific contract will describe the Sponsor's indemnification of the Investigator and institution for the duration of this study. Additional indemnification or insurance will be provided as required by local regulations.

14. FINANCIAL STATEMENT

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

15. PUBLICATION POLICY

All protocol, amendment, and related information, except for that disclosed by the Sponsor on public registry websites, is considered confidential information of the Sponsor.

On completion of the study, data will be analyzed per the SAP, and a CSR will be prepared. Study results will be disclosed via public registry website, and a lay language summary will be made available per applicable local regulations. The Sponsor does not plan to make publicly available the full CSR, the anonymized participant-level dataset, or the statistical code for generating the results.

The results of this study may be published or presented by the Sponsor. Data relating to this study may not be presented by any Investigator without prior permission from the Sponsor.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements.

16. LITERATURE REFERENCES

1. Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. Sep 1 2018;198(5):e44-e68. doi:10.1164/rccm.201807-1255ST
2. Urteaga MB, Ruz JR, González MS. Idiopathic pulmonary fibrosis. *Radiologia (Engl Ed)*. Dec 2022;64 Suppl 3:227-239. doi:10.1016/j.rxeng.2022.10.009
3. Munchel JK, Shea BS. Diagnosis and management of idiopathic pulmonary fibrosis. *R I Med J (2013)*. Sep 1 2021;104(7):26-29.
4. Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. Mar 15 2011;183(6):788-824. doi:10.1164/rccm.2009-040GL
5. Königshoff M, Kramer M, Balsara N, et al. WNT1-inducible signaling protein-1 mediates pulmonary fibrosis in mice and is upregulated in humans with idiopathic pulmonary fibrosis. *J Clin Invest*. Apr 2009;119(4):772-87. doi:10.1172/jci33950
6. Spagnolo P, Cottin V. Genetics of idiopathic pulmonary fibrosis: from mechanistic pathways to personalised medicine. *J Med Genet*. Feb 2017;54(2):93-99. doi:10.1136/jmedgenet-2016-103973
7. Bellaye PS, Kolb M. Why do patients get idiopathic pulmonary fibrosis? Current concepts in the pathogenesis of pulmonary fibrosis. *BMC Med*. Sep 24 2015;13:176. doi:10.1186/s12916-015-0412-6
8. Wolters PJ, Collard HR, Jones KD. Pathogenesis of idiopathic pulmonary fibrosis. *Annu Rev Pathol*. 2014;9:157-79. doi:10.1146/annurev-pathol-012513-104706
9. Galli JA, Pandya A, Vega-Olivo M, Dass C, Zhao H, Criner GJ. Pirfenidone and nintedanib for pulmonary fibrosis in clinical practice: Tolerability and adverse drug reactions. *Respirology*. Aug 2017;22(6):1171-1178. doi:10.1111/resp.13024
10. Cilli A, Uzer F. Disease progression in idiopathic pulmonary fibrosis under anti-fibrotic treatment. *Sarcoidosis Vasc Diffuse Lung Dis*. Sep 13 2023;40(3):e2023034. doi:10.36141/svdld.v40i3.14048
11. Richeldi L, Azuma A, Cottin V, et al. Nerandomilast in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. Jun 12 2025;392(22):2193-2202. doi:10.1056/NEJMoa2414108
12. George PM, Patterson CM, Reed AK, Thillai M. Lung transplantation for idiopathic pulmonary fibrosis. *Lancet Respir Med*. Mar 2019;7(3):271-282. doi:10.1016/s2213-2600(18)30502-2
13. Graham BL, Brusasco V, Burgos F, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. *Eur Respir J*. Jan 2017;49(1)doi:10.1183/13993003.00016-2016
14. Swigris J, Cutts K, Male N, Baldwin M, Rohr KB, Bushnell DM. The Living with Pulmonary Fibrosis questionnaire in progressive fibrosing interstitial lung disease. *ERJ Open Res*. Apr 2021;7(2)doi:10.1183/23120541.00145-2020

Appendix 1. Investigator Agreement Page

Protocol Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of MTX-463 in Participants with Idiopathic Pulmonary Fibrosis (IPF)

Protocol Version	Version 2.0
Date of Protocol	15 December 2025

Name of Principal/Coordinating Investigator(s)

First name, last name, degrees
Principal Investigator

Date

Appendix 2. Study Contact Information

Name, title, address, and telephone number(s) of the Sponsor's responsible medical officer	PPD PPD Mediar Therapeutics 20 Overland Street, Suite 520 Boston MA 02215 PPD PPD

Appendix 3. Acceptable Methods of Contraception

Birth control methods that may be considered highly effective per the Clinical Trials Coordination Group *Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials version 1.2* include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner[1]
- Sexual abstinence[2]

[1] Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the participant and that the vasectomized partner has received medical assessment of the surgical success.

[2] Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

For the purpose of this document, a female is considered of childbearing potential (i.e., fertile), following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in participants not using hormonal contraception or hormonal replacement therapy. For the purpose of this document, a male is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

All participants of reproductive potential in the study must do the following:

- Female participants of childbearing potential must use a highly effective contraceptive method during the treatment and until 5 half-lives or 125 days after the last dose of study drug, whichever is longer.

- Male participants with female partners of childbearing potential must use condoms during the treatment and until 5 half-lives or 125 days after the last dose of study drug, whichever is longer.
- Participants completing the study as scheduled will be instructed to continue to perform monthly pregnancy testing at home for 3 months after completing the study. Those who discontinue the study early will be instructed to perform monthly pregnancy tests for 5 months after the last infusion of study drug. All participants will be informed to contact the study site immediately in the event of a positive pregnancy test.