Clinical Study Protocol

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A Phase IIb Study to Evaluate the Efficacy, Safety, and Tolerability of AZD8965 in Participants with Idiopathic Pulmonary Fibrosis (IPF) (ARGiNAUT)

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This protocol has been subject to a peer review according to AstraZeneca Standard procedures. The protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Standard - Bioethics and in compliance with prevailing laws and regulations.

Redacted for Public Disclosure

Version Scope: Global

Brief Title:

A Phase IIb study to evaluate AZD8965 in participants with IPF.

Study Phase: Phase IIb

Acronym: ARGiNAUT

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
AE(s)	Adverse event(s)
AESI(s)	Adverse event of special interest(s)
ALARA	As Low as Reasonably Achievable
ALAT	Latin American Thoracic Society
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ARG-1	Arginase-1
ARG-2	Arginase-2
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AxMP	Auxiliary Medicinal Products
BiPAP	Bilevel positive airway pressure
CCI	CCI
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence interval
CID	Clinical importance difference
CCI	CCI
Cmax	Maximum concentration
CMV	Cytomegalovirus
CNS	Central Nervous System
CPAP	Continuous positive airway pressure
CRO	Contract Research Organization
CSR	Clinical Study Report
CT	Computed Tomography
Ctrough	Trough concentration
DAEs	Discontinuation AEs
DES	Data Entry Site
DILI	Drug-Induced Liver Injury
D_{LCO}	Diffusing Capacity of the Lungs for Carbon Monoxide
DNA	Deoxyribonucleic Acid

Abbreviation or special term	Explanation
DUS	Disease Under Study
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECM	Extracellular matrix
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
CCI	CCI
ePRO	Electronic Patient Reported Outcome
ERS	European Respiratory Society
ETV	Early termination visit
EU	European Union
FAS	Full Analysis set
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FSH	Follicle-stimulating hormone
FU	Follow-Up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HAV	Hepatitis A virus
h	Hour(s)
Hb	Hemoglobin
HBc	Hepatitis B Core
HBcAb	Hepatitis B Core Antibody
HBS	Human Biological Samples
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEV	Hepatitis E virus
HIV	Human immunodeficiency virus
HR	Heart Rate
HRCT	High-Resolution Computed Tomography

Abbreviation or special term	Explanation
HSV	Herpes Simplex Virus
IAC	Independent Adjudication Committee
IATA	The International Air Transport Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin-6
ILD	Interstitial lung disease
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important protocol deviation
IPF	Idiopathic Pulmonary Fibrosis
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IRT/RTSM	Interactive Response Technology/ Randomization and Trial Supply Management
IUD	Intrauterine Device
IV	Intravenous
IVF	In vitro fertilization
JRS	Japanese Respiratory Society
LABA	Long-acting β2-agonist
LAMA	Long-acting muscarinic antagonist
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LOQ	Limit of Quantification
CCI	CCI [redacted]
LSLV	Last subject last visit
MAR	Missing at random
CCI	CCI [redacted]
CCI [redacted]	CCI [redacted]
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MoA	Mechanism of Action
CCI	CCI
CCI	CCI
PCR	Polymerase Chain Reaction
CCI	CCI
CCI	CCI
PI	Principal Investigator
PK	Pharmacokinetics
PKS	PK Analysis set
PRO	Patient Reported Outcome
QT	ECG interval measured from the onset of the QRS complex to the end of the T-wave
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTLs	Quality Tolerance Limits
RNA	Ribonucleic Acid
SABA	Short-acting β_2-agonist
SAE(s)	Serious Adverse Event(s)
SAF	Safety Analysis set
SAMA	Short-acting muscarinic antagonist
SAP	Statistical Analysis Plan
CCI	CCI
SoA	Schedule of Assessments
SPFQ	Study Participant Feedback Questionnaire
SpO2	Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TBL	Total Bilirubin
TE	Target engagement
TK	Toxicokinetic
CCI	CCI
UIP	Usual interstitial pneumonia
ULN	Upper Limit of Normal

Abbreviation or special term	Explanation
URC	Unblinded Review Committee
USA	United States of America
UV	Unscheduled visit
WOCBP	Women of Childbearing Potential
% predicted FVC	Percent Predicted Forced Vital Capacity

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title:

A Phase IIb Study to Evaluate the Efficacy, Safety, and Tolerability of AZD8965 in Participants with Idiopathic Pulmonary Fibrosis (IPF) (ARGiNAUT).

Brief Title:

A Phase IIb Study to Evaluate AZD8965 in Participants with Idiopathic Pulmonary Fibrosis (IPF)

Regulatory Agency Identifier Number(s):

Registry	ID
EU CT Number	2025-525016-41-00
IND	170314

Rationale:

AZD8965 is an oral small-molecule arginase inhibitor being developed for the treatment of IPF.

This Phase IIb study aims to evaluate the efficacy, safety, and tolerability of 3 doses of AZD8965 treatment administered CCI compared to placebo in participants with IPF, including those on antifibrotic therapy (nintedanib, pirfenidone, nerandomilast), either alone or in combination, or in those not on antifibrotic therapy.

Objectives, Endpoints, and Estimands:

The following information relates to the objectives of the study and the rationale behind their selection.

Objectives	Endpoint and estimands *
Primary	
To evaluate the clinical efficacy of AZD8965 compared with placebo on the absolute change from baseline in FVC in mL at Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo. **Endpoint**: change from baseline in FVC (mL) at Week 24 **Population-level-summary measure**: Differences in mean change from baseline in FVC between AZD8965 and placebo. **Strategy for intercurrent events**: Three intercurrent events are defined: 1) change in planned antifibrotic treatment; 2) IMP treatment discontinuation; 3) death or lung transplant. The following strategy will be used for intercurrent events (ICH E9 [R1]): • Intercurrent events (except for death or lung transplant) will be handled via a CCI (ie, the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs). • Intercurrent events of death or lung transplant will be handled via a composite strategy in which their FVC values will be replaced CCI CCI in the same treatment arm. **Supportive estimand**: While-on-treatment.

Objectives	Endpoint and estimands *
Secondary	
To evaluate the relationship between dose and clinical efficacy of AZD8965 based on the absolute change from baseline in FVC in mL at Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo. **Endpoint**: change from baseline in FVC (mL) at Week 24. **Population-level-summary measure**: Differences in mean change from baseline in FVC between AZD8965 and placebo and [redacted] **Strategy for intercurrent events**: Three intercurrent events are defined: 1) change in planned antifibrotic treatment; 2) IMP treatment discontinuation; 3) death or lung transplant. The following strategy will be used for intercurrent events (ICH E9 [R1]): • Intercurrent events (except for death or lung transplant) will be handled via a [redacted] (ie, the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs). • Intercurrent events of death or lung transplant will be handled via a composite strategy in which their FVC values will be replaced based on [redacted] the same treatment arm.

Objectives	Endpoint and estimands *
To evaluate the clinical efficacy of AZD8965 compared with placebo on the absolute change from baseline in % predicted FVC at Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo. **Endpoint**: change from baseline in % predicted FVC at Week 24. **Population-level-summary measure**: Difference in mean change from baseline in % predicted FVC between AZD8965 and placebo and CCI [redacted] CCI [redacted] **Strategy for intercurrent events**: Three intercurrent events are defined: 1) change in planned antifibrotic treatment; 2) IMP treatment discontinuation; 3) death or lung transplant. The following strategy will be used for intercurrent events (ICH E9 [R1]): • Intercurrent events (except for death or lung transplant) will be handled via a CCI [redacted] (ie, the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs). • Intercurrent events of death or lung transplant will be handled via a composite strategy in which their FVC values will be replaced based on CCI [redacted] CCI [redacted] in the same treatment arm. **Supportive estimand**: While-on-treatment.

Objectives	Endpoint and estimands *
To evaluate the clinical efficacy of AZD8965 compared with placebo on the rate of decline in FVC (mL/week) at Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo. **Endpoint**: slope (rate of decline) in FVC (mL/week) from baseline to 24 weeks **Population-level-summary measure**: Difference in mean rate of decline in FVC between AZD8965 and placebo. CCI [redacted] **Strategy for intercurrent events**: Three intercurrent events are defined: 1) change in planned antifibrotic treatment; 2) IMP treatment discontinuation; 3) death or lung transplant. The following strategy will be used for intercurrent events (ICH E9 [R1]): • Intercurrent events (except for death or lung transplant) will be handled via a CCI [redacted] (ie, , the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs). • Intercurrent events of death or lung transplant will be handled via a composite strategy in which their FVC values will be replaced CCI [redacted] CCI [redacted] in the same treatment arm. **Supportive estimand**: While-on-treatment.
To assess the safety and tolerability of AZD8965 compared with placebo up to Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo and have post-baseline safety data (Safety Analysis Set). **Endpoints**: CCI [redacted], DAEs, SAEs, AESIs, vital signs, clinical laboratory assessments (eg, clinical chemistry, hematology, urinalysis, CCI [redacted] ECGs, CCI [redacted] **Population-level-summary measure**: descriptive statistics (eg, absolute counts, frequencies).

Objectives	Endpoint and estimands *
To evaluate the PK CCI CCI of AZD8965	**Population**: all participants who received ≥ 1 dose of AZD8965 with at least one measurable plasma concentration above the LOQ (PKS) **Endpoint**: CCI AZD8965 plasma concentrations: timepoints specified in SoA tables. **Population-level summary measure**: summary statistics. **Strategy for intercurrent events**: while-on-treatment strategy. **Intercurrent event specification**: treatment discontinuation and any IPDs that may affect the PK blood samples or change in IPF background therapy

For exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol.

Overall Design Synopsis:

This is a Phase IIb, randomized, placebo-controlled, double-blind, parallel-group study to assess the efficacy, safety and tolerability of three doses of AZD8965 versus placebo administered orally CCI over a 24-week treatment period to participants with IPF. The enrolled participants will include those on stable dose(s) of one or two approved antifibrotic therapies and those who are not taking any antifibrotic therapy. Participants who are CCI CCI CCI

Approximately 360 participants will be randomized across approximately 200 sites globally and will be CCI CCI CCI. Background antifibrotic therapy usage is defined as follows:

- Participants receiving approved antifibrotic therapy (nintedanib, pirfenidone, or nerandomilast where locally approved) either alone or in combinations of either nintedanib and nerandomilast (either 9 mg or 18 mg BID) or pirfenidone and nerandomilast (at the 18 mg BID dose) (Section 6.1.1). Participants must be on stable dose(s) for at least 12 weeks before Screening and, if possible, throughout the study.
- Participants not receiving any antifibrotic therapy including those who have never initiated antifibrotic therapy and those who discontinued it at least 12 weeks before Screening (Section 5.3.4.2).

Participants meeting the eligibility criteria will be randomized in a CCI take placebo, AZD8965 CCI AZD8965 CCI or AZD8965 CCI An unblinded IDMC and a blinded IAC will be appointed for this study. The IDMC and IAC will each operate according to the agreed IDMC and IAC Charters, respectively.

Brief Summary:

This study aims to evaluate whether an investigational drug called AZD8965 can improve lung function including slow lung function decline in participants with IPF.

The term "Study Intervention" refers to AZD8965 throughout the protocol.

The study will recruit participants who are at least 40 years old and diagnosed with IPF. Participants must be either on a stable dose(s) of antifibrotic therapies (nintedanib, pirfenidone, and/or nerandomilast), either alone or in combination, or not currently receiving any antifibrotic medication (Section 6.1.1). Participants who are receiving antifibrotic medications are expected to continue taking these medications at the same dose(s) during the study.

Participants are expected to be in the study for approximately 31 weeks. Screening assessments can be performed on one or multiple days during the Screening period. Participants who meet all eligibility requirements will proceed to CCI the assessments may be performed CCI if needed, and eligible participants will be randomly assigned to receive 1 of 3 AZD8965 doses or placebo.

Number of Participants:

Approximately 360 participants will be randomized into the study to have approximately CCI evaluable participants at Week 24.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened to determine whether they are eligible for the study, but are not randomly assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

Study Arms, Duration, and Visits:

Eligible participants with IPF will be randomized in a CCI to the following arms, respectively:

- Placebo for AZD8965 CCI
- AZD8965 CCI
- AZD8965 CCI
- AZD8965 CCI

CCI CCI CCI CCI

The total duration of the study for a participant is approximately 31 weeks, and treatment is CCI CCI

Screening (CCI): After participants provide informed consent, data required for determination of eligibility will be collected, and inclusion/exclusion criteria evaluated. The Screening period may be extended by CCI for a total duration of CCI if the Screening assessments cannot be reasonably completed in CCI .

Double-blind, placebo-controlled treatment (24 weeks): Eligible participants will be randomized in a CCI to receive placebo, AZD8965 CCI AZD8965 CCI , or AZD8965 CCI respectively, for 24 weeks (Week 0 to Week 24).

Follow-up: Participants will have follow-up assessments at approximately CCI CCI after the completion of the treatment period).

Number of Visits for Participants With vs Without CCI .

- For participants without CCI CCI at Screening, there are a total of CCI visits during the study. During the treatment period, visits will occur at CCI CCI
- For participants with CCI CCI at Screening, CCI CCI and CCI during the treatment period (with a total of CCI during the study) are required.

Additional Visits (all participants):

- Unscheduled visit(s) may be added to assess potential safety issues as needed during the study.
- For participants permanently discontinuing AZD8965 or placebo early but who are willing to remain in the study, see Section 7.
- Participants who wish to withdraw from the study will be encouraged to complete all the assessments of the Early Termination Visit (unless they do not consent to do so), see SoA Table 1 and Section 7.

Sub-studies

This study includes 3 sub-studies.

- HRCT sub-study: details are provided in Section 8.2.2.2.
- PK sub-study (optional for applicable countries): details are provided in Section 8.5.1.3.
- TE sub-study (mandatory for applicable countries): details are provided in Section 8.5.3.

Data Monitoring / Other Committee: Yes

Independent Data Monitoring Committee

An external IDMC will be appointed to provide systematic and unbiased assessment of safety for the study. The IDMC will monitor the safety of the study participants and the scientific integrity of the study and will make appropriate recommendations to AstraZeneca regarding further study conduct based on the available data. The IDMC may recommend modification or termination of the study based on reviewed data, including regular unblinded safety review. The IDMC may also conduct a CCI CCI The IDMC will operate according to an IDMC Charter; information about the composition of the committee and other details about the IDMC will also be included in the charter.

Independent Adjudication Committee

A blinded IAC with the expertise to evaluate acute exacerbations of IPF will be appointed. This panel will be comprised of independent clinical experts in the management of interstitial lung diseases and/or chest imaging.

Unblinded Review Committee

An URC may be appointed to review the IDMC output with details provided in a URC Charter.

Statistical Methods

- The study is powered on change from baseline in FVC (in mL) at Week 24.
- The analysis population for the efficacy endpoint analyses is the FAS defined as all randomized participants who received ≥ one dose of AZD8965 or placebo.
- The primary objective is to evaluate the effect of AZD8965 compared with placebo on the change from baseline in FVC (mL) CCI of treatment in participants with IPF. The change from baseline in FVC CCI in the AZD8965 dose groups will be compared with that observed in the placebo group using a CCI CCI Subsequently, these estimates will be used to perform the CCI CCI using the CCI CCI The CCI is used to assess whether a dose-response signal is present using a CCI CCI
- The CCI on change from baseline in FVC at Week 24 will be the primary analyses, and the CCI will be the secondary analyses.
- CCI CCI If implemented, the IDMC will CCI and make a

recommendation on whether the study will continue. CCI guidelines will be defined in an interim analysis SAP and the IDMC Charter prior to any CCI CCI

- Secondary assessments of efficacy will include the change from baseline in % predicted FVC CCI in participants with IPF. The AZD8965 dose group will be compared with placebo using a CCI to perform statistical testing and estimate the treatment effect CCI. The estimates will then be used to perform CCI
- Secondary assessments of efficacy will also include the rate of decline in FVC (mL/week) CCI. The AZD8965 dose group will be compared with placebo using CCI CCI The model will be used to perform statistical tests and estimate the CCI. CCI is also planned for this endpoint.

Sample Size Estimate and Justification:

Approximately 360 participants will be randomized into the study, aiming to have approximately CCI evaluable participants at Week 24. Participants will be randomized to placebo, AZD8965 CCI AZD8965 CCI or AZD8965 CCI in a CCI respectively. The study, when the sample sizes in the AZD8965 CCI and placebo are both CCI, will have at least CCI power to detect a difference in means of CCI between the AZD8965 CCI assuming that the common standard deviation ranges from CCI and using CCI with a CCI significance level.

Assuming CCI CCI CCI in change from baseline in FVC CCI AZD8965 CCI Week 24, the study would have at least CCI power to CCI based on the change from baseline in FVC at Week 24.

1.2 CCI



n = the number of evaluable participants at Week 24; the total number of randomized participants is approximately 360.
Background antifibrotic therapy/therapies include nintedanib, pirfenidone, and/or nerandomilast, either alone or in combination (see Section 6.1.1).
* Visits on CCI are only for participants with CCI at Screening.

1.3 Schedule of Activities

Table 1 Schedule of Activities

Procedure	Screening	Intervention Period [a]								Follow-up			Details in Protocol Section or Appendix
Visit [b]	CCI										**ETV** [g]	**UV** [h]	
Weeks													
Study Day													
Visit Window (days) [i]													
CCI													Section 5.2
Signed Informed Consent	X												Section 5.1, Appendix A 3
Signed Informed Consent for HRCT sub-study	X												Section 8.2.2.2
Signed Informed Consent for PK sub-study (for participants in applicable countries)	X												Section 8.5.1.3
Signed Informed Consent for optional Genomics Initiative Research (CCI CCI) [j]	X												Section 8.7
Inclusion and exclusion criteria	X	X											Section 5.1, Section 5.2
Medical and IPF history [k]	X												Section 8.1
Demographics	X												Section 8.1
Smoking history [l]	X	X	X		X		X	X	X				Section 8.1

Procedure	Screening	Intervention Period [a]								Follow-up			Details in Protocol Section or Appendix
Visit [b]	CCI										**ETV** [g]	**UV** [h]	
Weeks													
Study Day													
Visit Window (days) [i]													
Prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	Section 6.9
Height and weight [m]	X	X							X		X		Section 8.1
D_{LCO} corrected for hemoglobin [n]	X												Section 8.1.2
Chest HRCT central review for eligibility [o]	X												Section 8.2.2.1
Blood samples for FSH [p]	X												Section 8.3.4
Blood pregnancy test (WOCBP only)	X												Section 8.3.4
Urine pregnancy test (WOCBP only) [q]		X	X		X		X	X	X		X		Section 8.3.4
Dispense urine pregnancy test kit for home testing (WOCBP only)					X		X	X					Section 8.3.4.1
Urine pregnancy test at home with virtual visits (WOCBP only) [r]	CCI												Section 8.3.4.1
Vital signs (BP, HR, temperature, respiratory rate) and SpO_2	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.3.2
Physical examination [s]	X	X (brief)	X (brief)	X (brief)	X (brief)	X (brief)	X (brief)	X (brief)	X	X (brief)	X		Section 8.3.1
Safety 12-Lead ECG [t]	X	X	X		X		X	X	X	X	X		Section 8.3.3

Procedure	Screening	Intervention Period [a]								Follow-up	ETV [g]	UV [h]	Details in Protocol Section or Appendix
Visit [b]	CCI												
Weeks													
Study Day													
Visit Window (days) [i]													
Hepatitis A (IgM) and Hepatitis B serology (and Hepatitis B viral DNA but only for participants who are HBsAg negative and HBcAb positive at Screening)	X												Section 8.3.4
Hepatitis C serology (and also Hepatitis C viral RNA if Hepatitis C serology is positive at Screening)	X												Section 8.3.4
HIV serology	X												Section 8.3.4
Clinical Chemistry [u]	X	X	X	X	X	X	X	X	X	X	X		Section 8.3.4
Hematology [u]	X	X	X	X	X	X	X	X	X	X	X		Section 8.3.4
CCI													Section 8.3.4
													Section 8.3.4
Randomization [v]		X											Section 6.3
CCI													Section 6.1
IMP compliance			X		X		X	X	X		X		Section 6.5
Study participant feedback questionnaire (optional) [w]		X					X		X		X		Section 8.11
Efficacy Assessments													
Clinic Spirometry [x, y]	X	X			X		X	X	X		X		Section 8.2.1

Procedure	Screening	Intervention Period [a]								Follow-up			Details in Protocol Section or Appendix
Visit [b]	CCI										**ETV** [g]	**UV** [h]	
Weeks													
Study Day													
Visit Window (days) [i]													
Safety Assessments													
Collection of AEs/SAEs/DAEs/AESIs	SAEs only	X	X	X	X	X	X	X	X	X	X	X	Section 8.4.1
CCI													Section 8.3.6, Appendix H
													Section 8.3.6.2, Appendix J
													Section 8.3.6.1 and Appendix I
Pharmacokinetics													
Plasma for AZD8965 PK (CCI – all participants)	CCI												Section 8.5.1, Section 8.5.2, Table 2
Plasma PK sample for all participants receiving background antifibrotic drugs [j]		X			X		X		X				Section 8.5.1, Table 2

Procedure	Screening	Intervention Period [a]								Follow-up			Details in Protocol Section or Appendix
Visit [b]	CCI										**ETV** [g]	**UV** [h]	
Weeks													
Study Day													
Visit Window (days) [i]													
CCI plasma for AZD8965 PK (CCI CCI (PK sub-study participants only in applicable countries) [j]	CCI												Section 8.5.1, Section 8.5.2, Table 3
CCI plasma for participants receiving background antifibrotic drugs (PK sub-study participants only in applicable countries) [j]					X								Section 8.5.1, Table 3
Exploratory Assessments													
Assessment of acute exacerbations of IPF	X	X	X	X	X	X	X	X	X	X	X	X	Section 8.2.3
Assessment of respiratory-related hospitalizations			X	X	X	X	X	X	X	X	X	X	Section 8.2.6
Supplemental oxygen use [aa]	X	X	X		X		X	X	X	X	X	X	Section 8.2.5
CCI													Section 8.2.4
													Section 8.2.4
													Section 8.2.4
													Section 8.2.2.2
Pre-dose plasma, serum, and whole blood CCI exploratory translational biomarker analyses [j, dd]		X							X				Section 8.8.1.1, Section 8.8.1.4

Procedure	Screening	Intervention Period [a]								Follow-up			Details in Protocol Section or Appendix
Visit [b]	CCI										**ETV** [g]	**UV** [h]	
Weeks													
Study Day													
Visit Window (days) [i]													
CCI													Section 8.5.2
Exploratory biomarkers (plasma and urine) [j]		X	X		X		X		X				Section 8.8.1.2, Section 8.8.1.3
Blood for Genomics Initiative (Gx) Optional, exploratory genetic sample [j]		X											Section 8.7

a. All assessments must be conducted prior to dosing except those that are specified as post-dose on days of dosing.
b. The visit schedule will always be calculated from the randomization date. Day 1 is defined as the calendar day of randomization.
c. Visit 1 assessments may be performed over more than one occasion during the CCI prior to randomization. If a participant is unable to complete the required Screening procedures within the CCI Screening period due to unforeseeable circumstances, delays in scheduling, or the need to repeat one or more tests, Screening may be extended for up to an additional CCI
d. CCI assessments may be performed over CCI
e. CCI are CCI .
f. CCI are required between CCI
g. The ETV is the last visit for participants who discontinued IMP and will withdraw from the study. The ETV should be performed CCI after discontinuation of the IMP. The ETV is not performed for participants who discontinued IMP but will remain in the study.
h. Unscheduled visit(s) may be conducted to assess safety issues as needed during the study. The investigator will determine which assessments will be completed based on the reason for the unscheduled visit and considerations for participant safety.
i. All visit windows are relative to the study day for each visit stated in the SoA.
j. CCI
k. Medical and IPF history will be recorded in eCRF.

l. Smoking history will be collected at Screening (never smoker, former smoker, active smoker [including number of packs smoked per day], pack-years of smoking, and years since quitting smoking) and at all visits during the treatment period; these data will be recorded in the eCRF.

m. Height will be measured at Screening only. Height and weight should be measured with the participant not wearing shoes.

n. Historical D_{LCO} results within CCI of Screening may be used.

o. A HRCT scan with central reading (either a historical scan or a new scan) will be required for all participants during the Screening period to determine eligibility. For participants without a historical HRCT scan within CCI of Screening, a new HRCT scan will be performed during the Screening period after other key eligibility criteria are confirmed, allowing 5 business days for central reading prior to CCI For participants who had a historical HRCT scan within CCI of Screening and whose scan meets the quality requirements of this study, the historical HRCT images may be submitted for central reading for eligibility before other key eligibility criteria are confirmed. If central reading of the historical HRCT scan confirms a diagnosis of IPF, no new HRCT scan is needed during Screening. To conduct an HRCT within the trial, all applicable local regulatory requirements must be satisfied.

p. Applicable only to postmenopausal women < 55 years of age. Historical FSH values are acceptable if available in the participant's medical record.

q. A urine pregnancy test will be performed for WOCBP at least every 4 weeks. The test will be performed in-clinic on CCI , and the ETV. The result of urine pregnancy tests performed in-clinic must be available prior to dosing. A confirmatory serum pregnancy test will be performed for any positive urine pregnancy test post-randomization.

r. A home urine pregnancy test will be performed by WOCBP on CCI and the participants must report the results of home urine pregnancy test via virtual visits with the site on the day that they perform the test. All urine pregnancy test results will be recorded in eCRF. Participants with a positive home urine pregnancy test will be instructed by their site to withhold IMP dosing while awaiting confirmation of pregnancy and assessed in the clinic via an UV. A confirmatory serum pregnancy test will be performed for any positive urine pregnancy test post-randomization.

s. A brief physical examination will be conducted at all visits, except for a full examination at Screening, CCI and ETV (and UV if indicated). A full examination may be done at other visits if deemed necessary by the PI or delegate. The brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

t. Participants must be in the supine position and resting for ≥ 10 minutes before the 12-lead ECG. Triplicate 10-second 12-lead ECGs will be obtained at all visits and timepoints per the SoA. ECGs will be assessed pre-dose, and at other times clinically indicated.

u. These assessments may also be conducted at other times if clinically indicated. CCI CCI on clinical chemistry or hematology laboratory testing.

v. Eligible participants may be randomized after their Screening assessments have been completed and all eligibility criteria have been confirmed.

w. SPFQ will be performed only in countries/sites where approved for use. Consent to the SPFQ will be captured in the ePRO electronic device. If possible, the remaining (previously unadministered) parts of the SPFQ should be completed at the ETV, if the participant withdraws early from the study.

x. Expedited central overread of spirometry data will be used at CCI If spirometry quality is not acceptable by central overread, the participant will be re-tested either on the same day (if the maximum number of allowed FVC efforts in one day [8 attempts] has not been exceeded) or another day.

y. Participants who are hospitalized or experiencing an acute exacerbation of IPF at planned study visits should not perform spirometry assessments until they have fully recovered in the opinion of the investigator. Details are found in Section 8.2.1.7.

z. CCI

aa. Supplemental oxygen use at rest, during sleep, or with activity will be recorded in the eCRF and in the concomitant medications list. The date of supplemental oxygen initiation will be documented in the eCRF.

bb. During clinic visits, the ePRO questionnaires must be administered prior to the administration of the study treatment. ePRO questionnaires must be administered in the following order: CCI CCI

cc. For the HRCT sub-study, the baseline scan must be either a new scan during the screening period or a historical scan within CCI of CCI that meet the scan requirements. The HRCT scan at CCI will only be performed on participants in the HRCT sub-study (in selected countries) who have a baseline HRCT for which the image quality meets quantitative analysis requirement confirmed by the central imaging vendor. CCI HRCT may be performed within 7CCI and should use the same scanner and settings as the baseline HRCT scan. If a participant experiences an acute exacerbation of IPF, a pneumonia, or a respiratory-related hospitalization during the study or discontinues IMP before CCI, the HRCT scan CCI not be performed and the participant will be discontinued from the HRCT sub-study. To conduct an HRCT scan within the trial, all applicable local regulatory requirements must be satisfied. Refer to Section 8.2.2.2 for more details

dd. CCI all participants (CCI) must avoid eating for at least CCI before pre-dose sample collection, and the time of the participant's last meal before sample collection will be recorded in the eCRF. CCI will be excluded from the exploratory biomarker and CCI

ee. CCI participants in the TE sub-study must avoid eating for at least CCI before pre-dose sample collection, and the time of the participant's last meal before sample collection will be recorded in the eCRF.

Table 2 PK Sampling Schedule for All Participants

	CCI				Details in Protocol Section or Appendix
Plasma AZD8965 (CCI CCI) PK sample taken pre-dose of the IMP [a, c]		X	X	X	Section 8.5.1, Section 8.5.1
Plasma PK sample(s) taken pre-dose(s) of antifibrotic drugs [b, c]	X	X	X	X	Section 8.5.1

a. At CCI all participants should aim to withhold their morning dose of IMP. After the PK blood sample is collected, participants should take their morning dose of IMP at the study site. Participants will then resume their normal schedule for taking IMP. See Section 8.5.1 for details.
b. At CCI participants who are taking background antifibrotic drug(s) (CCI) should aim to withhold their morning dose(s) of nintedanib, pirfenidone and/or nerandomilast. After the PK sample(s) are collected, participants should then take their dose of antifibrotic drug(s). Participants will then resume their normal schedule for all background antifibrotic drugs. See Section 8.5.1 for details.
c. The date and time of the most recent dose of IMP and antifibrotic drug and all PK sample collections must be recorded in the eCRF.

All participants will have PK samples collected pre-dose at CCI preferably in the morning (for those participants who are unable to attend the clinic in the morning, see section 8.5.1 for further details). PK sampling will assess concentrations of AZD8965 (CCI In participants receiving background antifibrotic therapy, additional pre-dose samples at CCI will be analyzed for pirfenidone, nintedanib, and/or nerandomilast concentrations (see Table 2).

It is essential to record the time of the last dose of AZD8965 and, when applicable, pirfenidone, nintedanib, and/or nerandomilast in the eCRF.

Table 3 PK Sampling Schedule for Participants in the PK Sub-study

	CCI				Details in Protocol Section or Appendix
Plasma AZD8965 CCI CCI PK sampling [a, b, e]		X pre-IMP dose and CCI CCI	X pre-IMP dose	X pre-IMP dose	Section 8.5.1, Section 8.5.1
Plasma PK sampling of antifibrotic drugs [c, d, e]	X (pre-dose antifibrotic drug)	X pre-dose antifibrotic drug dose CCI CCI CCI CCI	X (pre-dose antifibrotic drug dose)	X (pre-dose antifibrotic drug dose)	Section 8.5.1

a. At CCI all participants should withhold their morning dose of IMP. After the PK blood sample is collected, participants should take their first daily dose of IMP CCI at the study site. Participants will then resume their normal schedule for IMP intake.

b. At CCI additional CCI for the CCI of AZD8965 will be collected at CCI CCI (CCI CCI) as described in Section 8.5.1.

c. At CCI participants who are taking background antifibrotic drug(s) (CCI) should aim to withhold their morning dose(s) of nintedanib, pirfenidone and/or nerandomilast. After CCI has/have been taken, participants should then take their first daily dose of antifibrotic drug(s) (CCI as per the participant's routine). Participants will then resume their normal schedule for all background antifibrotic drugs. Details can be found in Section 8.5.1.

d. At CCI additional CCI for antifibrotic drugs will be collected CCI with the antifibrotic drug(s) CCI CCI as per the participant's routine). Details can be found in Section 8.5.1.

e. The date and time of the most recent dose of IMP and antifibrotic drugs, and CCI must be recorded in the eCRF.

Participants in PK sub-study will have CCI in the morning, prior to IMP administration (pre-dose). In addition, CCI will be collected at CCI At the same CCI timepoint, CCI will also be collected for pirfenidone, nintedanib, and/or nerandomilast in participants receiving these medications (Table 3). To ensure accurate interpretation of PK data concentration, it is essential to record the time of the last dose of IMP and, when applicable, pirfenidone, nintedanib, and/or nerandomilast and the time of any PK sample collection in the eCRF at all visits for the PK sub-study, including the timepoints at CCI

2 INTRODUCTION

AZD8965 is an oral selective inhibitor of ARG-1 and ARG-2 activity and is being developed for the treatment of IPF through inhibition of arginase activity. ARG-1 and ARG-2 are enzymes that convert arginine to ornithine, and ornithine can be further metabolized into proline, a major building block of interstitial collagens. Interstitial collagens are the most abundant protein in ECM and are deposited by myofibroblasts in the lungs of patients with IPF. Increased ARG-1 levels occur in the lungs of patients with IPF. In a murine model of pulmonary fibrosis in which mice were challenged with bleomycin and then treated therapeutically with AZD8965 versus vehicle, AZD8965 reduced the accumulation of interstitial collagen in the lungs of the bleomycin-challenged mice. Thus, AZD8965 has potential to slow disease progression in patients with IPF by reducing interstitial collagen synthesis and deposition by myofibroblasts.

2.1 Study Rationale

The purpose of this study is to evaluate the efficacy, safety, and tolerability of three doses of AZD8965 administered orally CCI compared to placebo in participants with IPF, including those on locally approved antifibrotic therapies (ie, nintedanib, pirfenidone, and/or nerandomilast) either alone or in combination (see Section 6.1.1) or those not on antifibrotic therapy. AZD8965 inhibits arginase, a key enzyme involved in interstitial collagen synthesis and deposition within the lung parenchyma of patients with IPF. Thus, arginase represents a promising therapeutic target for patients with IPF.

2.2 Background

IPF is a rare, chronic and progressive fibrosing ILD with a poor prognosis and a median survival of approximately 4.5 years from time of diagnosis (Tran et al 2020). Cardinal symptoms include dyspnea and a dry cough. The natural history of IPF is characterized by worsening of dyspnea, reduced exercise capacity, lung function decline, deterioration in quality of life, and ultimately death from respiratory failure (Lederer and Martinez 2018).

Pirfenidone, nintedanib, and nerandomilast were each approved to treat patients with IPF on the basis of reducing FVC decline (Richeldi et al 2014, King et al 2014, Karimi and Chowdhury 2015, Richeldi et al 2025). However, these therapies are associated with troublesome gastrointestinal side effects, which limit medication persistence (CCI [redacted] Importantly, these therapies do not improve quality of life, reduce symptoms or halt lung function decline, thus highlighting the pressing clinical unmet need in IPF.

A dysfunctional repair response (with fibrosis) resulting from repetitive alveolar epithelial injury is hypothesized to play a key role in the pathogenesis of IPF (Wilson and Wynn 2009). This leads to excessive accumulation of ECM, distortion of alveolar architecture, and loss of

lung function (Plantier et al 2018). Interstitial collagens are the most abundant proteins in the ECM and are deposited by myofibroblasts, which are the key effector cells in IPF.

Dysregulation of the arginase pathway due to increased levels of ARG-1 in the lung is a potential mechanism that contributes to the pathogenesis of IPF. ARG-1 is a key enzyme involved in the conversion of arginine into ornithine, which is a precursor of proline (Heuser et al 2025). High levels of ARG-1 and/or arginine metabolites have been found in bronchoalveolar fluid, alveolar macrophages, and explanted lung tissue derived from patients with IPF (Mora et al 2006, Zhao et al 2017). Proteomics on laser-capture micro dissected lung tissue from patients with IPF, identified ARG-1 as one of the highest differentially expressed proteins with greater expression in fibrotic regions compared with non-fibrotic areas (Herrera et al 2022). Furthermore, metabolite profiling of plasma showed significantly higher L-ornithine levels in 300 participants with IPF in the IPF Prospective Outcomes Registry, compared with 100 controls (Summer et al 2024). However, plasma L-ornithine levels were similar in participants with IPF who were taking antifibrotic therapies and those who were not, suggesting that the arginase pathway remains upregulated despite the use of antifibrotic therapies. Thus, by inhibiting arginase, AZD8965 has potential to be efficacious either when taken in combination with antifibrotic medications or as monotherapy in patients with IPF.

To date, there have been no clinical studies evaluating arginase inhibitors in participants with IPF. However, inhibition of arginase prevents bleomycin-induced interstitial collagen accumulation in the lungs of rodents (Grasemann et al 2015; Wu et al 2016, Yadav et al 2025).

This Phase IIb study aims to assess the efficacy, safety, and tolerability of AZD8965 in participants with IPF, including those taking and those not taking approved antifibrotic therapy.

A detailed description of the chemistry and pharmacology of AZD8965 is provided in the AZD8965 IB.

2.3 Benefit/Risk Assessment

More detailed information about the expected benefits and risks and reasonably expected AEs of AZD8965 may be found in the AZD8965 IB.

In a Phase I clinical study in healthy participants (D6960C00001), AZD8965 CCI [redacted] AZD8965 CCI [redacted] There were CCI [redacted], and all participants completed the study.

CCI [redacted] have been identified as potential risks from nonclinical studies, and CCI [redacted] is a theoretical risk related to

AZD8965's mechanism of action. No safety concerns related to these effects were observed in the healthy participant Phase I study.

2.3.1 Risk Assessment

To date, there are no identified risks associated with the use of AZD8965 in humans. Potential risks for AZD8965 are described in Table 4.

Table 4 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: AZD8965		
CCI CCI CCI	AZD8965 inhibits ARG-1, which converts ammonia to urea in the liver as part of the urea cycle, raising potential concerns based on the CCI characteristic of severe inherited ARG-1 deficiency in which affected individuals have < 1% of the normal amount of arginase in their cells. However, this risk is deemed low. The CCI within hepatocytes CCI CCI AZD8965 CCI ; AZD8965 CCI CCI within these cells. Furthermore, clinical data from two other extracellular arginase inhibitors (CCI) did not demonstrate any CCI consistent with CCI in participants with cystic fibrosis or advanced cancers over 14 days of dosing and a median of 56 days of dosing, respectively CCI CCI CCI Nonclinical GLP studies with AZD8965 in CCI CCI CCI CCI Elevated CCI and CCI levels normalized CCI . No safety signals related to CCI associated with CCI were observed following CCI CCI healthy participants in the Phase I study (D6960C00001).	Participants with CCI CCI CCI CCI CCI CCI will be excluded (see Section 5.2, Exclusion Criterion 5 and 11). CCI CCI CCI CCI CCI CCI CCI CCI CCI CCI will be classified CCI (see Section 8.4.3).
CCI	CCI CCI CCI CCI CCI (AZD8965 IB Section 4.3).	Participants with CCI CCI will be excluded (Eligibility Criterion 13) Participants will undergo CCI CCI during the study by measuring CCI CCI and performing

Table 4 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Based on CCI (AZD8965 IB Section 4.2), it is anticipated that the risk of clinically significant CCI is low in participants with IPF receiving the doses to be evaluated in this study (D6960C00005). In the Phase I study (D6960C00001), there were CCI safety signals observed CCI in healthy volunteers.	CCI CCI CCI (Table 1). CCI CCI CCI CCI (Table 1). CCI is classified as an CCI (Section 8.4.3).
CCI	This is a CCI CCI CCI CCI (AZD8965 IB Section 4.3). In the CCI CCI CCI (no recovery period was included), there was an CCI CCI CCI CCI (AZD8965 IB Section 4.3). Serious and non-serious CCI were reported in monotherapy cohorts treated in the CCI CCI). However, given the limited available data, it remains unclear to what extent the severity of underlying disease in participants with advanced or metastatic cancers or the standard of care treatments that they had received may have contributed to these events. No AEs classified under the system organ class CCI CCI CCI CCI	Participants with a CCI CCI CCI CCI prior to or during Screening will be excluded (Exclusion Criterion 14). Participants will undergo laboratory monitoring such CCI and clinical chemistry CCI CCI testing if clinically indicated) (Table 1) CCI is classified as an CCI (see Section 8.4.3).

Table 4 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	No safety signals related to CCI were observed CCI CCI in healthy participants in the Phase I study (D6960C00001).	

2.3.2 Benefit Assessment

No clinical data on AZD8965 in participants with IPF are available to assess actual benefits of AZD8965, and it is possible that some individual participants in this study may not benefit. However, the potential benefits expected for AZD8965 in individuals with IPF are based on: 1) the mechanism of action of AZD8965; 2) pre-clinical data showing that AZD8965 treatment inhibited arginase activity in the lungs and this was associated with reduced pulmonary fibrosis in bleomycin-challenged mice; CCI CCI see AZD8965 IB) CCI AZD8965 CCI ; and 4) data from prior clinical studies of other drugs with antifibrotic activities showing that they reduce disease progression in participants with IPF, including decreased FVC decline, respiratory-related hospitalizations, and acute exacerbations of IPF.

Further information about potential benefits and risks of AZD8965 is included in the AZD8965 IB.

2.3.3 Overall Benefit/Risk Conclusion

Based on the MoA and pre-clinical data, AZD8965 is expected to slow the decline in lung function and stabilize symptoms and quality of life in participants with IPF.

The key potential risks associated with arginase inhibition include CCI CCI AZD8965 CCI CCI None of these risks were observed clinically in Phase I studies conducted in healthy volunteers.

Considering the measures taken to minimize risk to participants in this study, the potential risks of AZD8965 are acceptable relative to the anticipated clinical benefits in IPF. Based on this, the benefit/risk assessment for AZD8965 appears favorable.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 5 Objectives and Endpoints

Objectives	Endpoint and Estimands
Primary	
To evaluate the clinical efficacy of AZD8965 compared with placebo on the absolute change from baseline in FVC in mL at Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo. **Endpoint**: change from baseline in FVC (mL) at Week 24 **Population-level-summary measure**: Differences in mean change from baseline in FVC between AZD8965 and placebo. **Strategy for intercurrent events**: Three intercurrent events are defined: 1) change in planned treatment; 2) IMP treatment discontinuation; 3) death or lung transplant. The following strategy will be used for intercurrent events (ICH E9 [R1]): • Intercurrent events (except for death or lung transplant) will be handled via a CCI (ie, the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs). • Intercurrent events of death or lung transplant will be handled via a composite strategy in which their FVC values will be replaced based CCI in the same treatment arm. **Supportive estimand**: While-on-treatment.

Objectives	Endpoint and Estimands
Secondary	
To evaluate the relationship between dose and clinical efficacy of AZD8965 based on the absolute change from baseline in FVC in mL at Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo. **Endpoint**: change from baseline in FVC (mL) at Week 24. **Population-level-summary measure**: Differences in mean change from baseline in FVC between AZD8965 and placebo and CCI [redacted] **Strategy for intercurrent events**: Three intercurrent events are defined: 1) change in planned treatment; 2) IMP treatment discontinuation; 3) death or lung transplant. The following strategy will be used for intercurrent events (ICH E9 [R1]): • Intercurrent events (except for death or lung transplant) will be handled via a CCI [redacted] (ie, the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs). • Intercurrent events of death or lung transplant will be handled via a composite strategy in which their FVC values will be replaced based CCI [redacted] in the same treatment arm.

Objectives	Endpoint and Estimands
To evaluate the clinical efficacy of AZD8965 compared with placebo on the absolute change from baseline in % predicted FVC at Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo. **Endpoint**: change from baseline in % predicted FVC at Week 24. **Population-level-summary measure**: Difference in mean change from baseline in % predicted FVC between AZD8965 and placebo and CCI CCI CCI CCI **Strategy for intercurrent events**: Three intercurrent events are defined: 1) change in planned treatment; 2) IMP treatment discontinuation; 3) death or lung transplant. The following strategy will be used for intercurrent events (ICH E9 [R1]): • Intercurrent events (except for death or lung transplant) will be handled via a CCI (ie, the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs). • Intercurrent events of death or lung transplant will be handled via a composite strategy in which their FVC values will be replaced based on CCI in the same treatment arm. **Supportive estimand:** While-on-treatment.

Objectives	Endpoint and Estimands
To evaluate the clinical efficacy of AZD8965 compared to placebo on the rate of decline in FVC (mL/week) at Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo. **Endpoint**: slope (rate of decline) in FVC (mL/week) from baseline to 24 weeks. **Population-level-summary measure**: Difference in mean rate of decline in FVC between AZD8965 and placebo. CCI [redacted] **Strategy for intercurrent events**: Three intercurrent events are defined: 1) change in planned treatment; 2) IMP treatment discontinuation; 3) death or lung transplant. The following strategy will be used for intercurrent events (ICH E9 [R1]): • Intercurrent events (except for death or lung transplant) will be handled via a CCI [redacted] (ie, the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs). • Intercurrent events of death or lung transplant will be handled via a composite strategy in which their FVC values will be replaced based on CCI [redacted] in the same treatment arm. **Supportive estimand**: While-on-treatment.
To assess the safety and tolerability of AZD8965 compared with placebo up to Week 24	**Population**: all randomized participants who received ≥ 1 dose of AZD8965 or placebo and have post-baseline safety data (Safety Analysis Set). **Endpoints**: AEs, DAEs, SAEs, AESIs, vital signs, clinical laboratory assessments (eg, clinical chemistry, hematology, urinalysis, CCI [redacted] ECGs, CCI [redacted] **Population-level-summary measure**: descriptive statistics (eg, absolute counts, frequencies).

Objectives	Endpoint and Estimands
To evaluate the PK of the CCI CCI of AZD8965	**Population**: all participants who received ≥ 1 dose of AZD8965 with at least one measurable plasma concentration above the LOQ (PKS) **Endpoint**: CCI CCI of AZD8965plasma concentrations: timepoints specified in SoA tables. **Population-level summary measure**: summary statistics. **Strategy for intercurrent events**: while-on-treatment strategy. **Intercurrent event specification**: treatment discontinuation and any IPDs that may affect the PK blood samples or change in IPF background therapy
Exploratory – Not all exploratory endpoints will be reported in the CSR	
Exploratory Objectives	Endpoints
To evaluate the clinical efficacy of AZD8965 compared with placebo on the proportion of participants who initiated supplemental oxygen therapy up CCI	Proportion of participants who initiated supplemental oxygen therapy up to CCI
To evaluate the clinical efficacy of AZD8965 compared with placebo on the proportion of participants with a decrease from baseline in % predicted FVC ≥ 10% up CCI	Proportion of participants with ≥ 10% absolute decline in FVC (as % of predicted) CCI from baseline up CCI
To evaluate the clinical efficacy of AZD8965 compared with placebo on the proportion of participants with a decrease from baseline in % predicted FVC ≥ 5% up CCI	Proportion of participants with ≥ 5% absolute decline in FVC (as % of predicted) CCI from baseline up CCI
(HRCT sub-study only) To assess the effect of AZD8965 compared with placebo on the change from baseline HRCT imaging endpoints at CCI	CCI CCI CCI CCI
To assess the effect of AZD8965 compared with placebo on a combined endpoint of acute exacerbations of IPF, respiratory-related hospitalizations and all-cause mortality	Time to first event (adjudicated acute exacerbations of IPF; respiratory-related hospitalizations; all-cause mortality)
To assess the effect of AZD8965 compared to placebo on acute exacerbations of IPF	Time to first acute exacerbation of IPF (adjudicated acute exacerbations of IPF)

Objectives	Endpoint and Estimands
To assess the effect of AZD8965 compared to placebo on respiratory-related hospitalizations	Time to first respiratory-related hospitalization
To assess the effect of AZD8965 compared with placebo on CCI CCI CCI CCI CCI	CCI
To assess the effect of AZD8965 compared with placebo on CCI CCI CCI	
To assess the effect of AZD8965 compared with placebo on CCI CCI	
To assess the effect of AZD8965 compared with placebo on CCI CCI	
To assess the effect of AZD8965 compared with placebo on arginase pathway and IPF-related biomarkers from baseline up to CCI	Changes from baseline in gene expression or protein/peptide or metabolite biomarker levels in whole blood, serum, or plasma, including but not limited to: CCI CCI CCI CCI CCI CCI
CCI	CCI CCI CCI CCI
To assess the effect of AZD8965 compared with placebo on CCI CCI CCI	CCI CCI
To assess the effect of AZD8965 compared with placebo on CCI CCI CCI CCI CCI	CCI CCI CCI

Objectives	Endpoint and Estimands
To assess the effect of AZD8965 compared with placebo on [redacted]	[redacted]
To explore how multi-omics variations, including genetics, may affect clinical parameters, risk and prognosis of diseases and the response to medications as detailed in Appendix D Optional Genomics Initiative Note: The samples will be taken from consented participants for DNA isolation, blood derivatives and storage	Exploratory endpoints are related to the data generated from multi-omics analysis, including genetics which may be part or all of the participant's genetic information
To explore whether there is a change in the plasma concentration of locally approved antifibrotic drugs when taken with AZD8965 during the study	**Population**: all participants who received locally approved antifibrotic drugs (ie, pirfenidone, nintedanib, or nerandomilast) and ≥ 1 dose of AZD8965 or placebo ([redacted] **Endpoints**: pirfenidone, nintedanib, and/or nerandomilast plasma concentrations; at the timepoints specified in SoA tables
To explore whether there is a change in the plasma concentrations of [redacted] of AZD8965 in participants taking or not taking antifibrotic drugs	**Population**: all participants who received locally approved antifibrotic drugs (ie, pirfenidone, nintedanib, or nerandomilast) or not and ≥ 1 dose of AZD8965 with at least one measurable plasma concentration above the LOQ [redacted]f AZD8965 plasma concentrations; at the timepoints specified in SoA tables
To compare quality of spirometry data assessed by automated artificial intelligence with that assessed by central overread	Exploratory endpoints are related to the spirometry data generated by automated artificial intelligence and by central overread

Results of exploratory objectives may not be included in the CSR.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase IIb, randomized, placebo-controlled, double-blind, parallel-group study designed to evaluate the efficacy, safety, and tolerability of 3 doses of AZD8965 versus placebo tablets administered orally [redacted] over a 24-week treatment period to participants with IPF. Stable background antifibrotic therapy will be allowed (Section 6.1.1). Participants receiving background antifibrotic therapy must be on a stable dose for at least 12 weeks before Screening and are expected to remain on the same background antifibrotic therapy throughout the study. Participants not using any background antifibrotic therapy (either those who have never taken antifibrotic therapy or those who discontinued antifibrotic therapy at least 12 weeks prior to Screening) are also eligible and are expected to not initiate background antifibrotic therapy during the study (Section 5.3.4.2).

The study is planned to take approximately 31 weeks for each participant, comprising of a [redacted] Screening period, a 24-week treatment period, and a FU visit at approximately [redacted] after the completion of the treatment period). The study will be conducted across approximately 200 sites globally.

Approximately 360 participants will be randomized into the study to have approximately [redacted] evaluable participants at Week 24. The study will recruit participants with IPF who are receiving treatment with locally approved antifibrotic therapy and have been on a stable dose for at least 12 weeks before Screening, or who are not receiving antifibrotic therapy (either naïve to treatment or having discontinued antifibrotic therapy at least 12 weeks before Screening).

Participants will be evaluated for study eligibility during a Screening period of [redacted]; see Section 8.1). Participants who do not meet the criteria for participation in this study (ie, screen failures) may be eligible for re-screening once for selected reasons (see Section 5.4).

The results of all screening assessments must be received and evaluated before randomization.

All participants meeting the eligibility criteria for the study will be randomized in a [redacted] to the following arms, respectively:

- Placebo for AZD8965 [redacted]
- AZD8965 [redacted]
- AZD8965 [redacted]
- AZD8965 [redacted]

CCI CCI CCI CCI. Background antifibrotic therapy usage is defined as follows:

- Participants receiving approved antifibrotic therapy (nintedanib, pirfenidone, or nerandomilast where locally approved) either alone or in combinations of either nintedanib and nerandomilast (either 9 mg or 18 mg BID) or pirfenidone and nerandomilast (at the 18 mg BID dose) (Section 6.1.1). Participants must be on stable dose(s) for at least 12 weeks before Screening and, if possible, throughout the study.
- Participants not receiving any antifibrotic therapy including those who have never taken antifibrotic therapy and those who discontinued it at least 12 weeks before Screening (Section 5.3.4.2).

The Screening assessments can be performed on one or multiple days during the Screening period. Participants who meet all eligibility requirements will proceed to CCI required assessments may be performed CCI if needed. Eligible participants will then be randomized to one of the following dosing regimens and to maintain blinding and mask dose levels across arms, all participants will take CCI CCI CCI CCI

- CCI AZD8965 CCI
- CCI CCI
- CCI AZD8965 CCI CCI CCI
- CCI AZD8965 CCI CCI CCI

Screening (CCI): After participants provide informed consent, data required for determination of eligibility will be collected, and inclusion/exclusion criteria will be evaluated. The Screening period may be extended CCI for a total duration CCI if the Screening assessments cannot be reasonably completed in CCI.

Double-blind, placebo-controlled treatment (24 weeks): Eligible participants will be randomized in a CCI to receive placebo, AZD8965 CCI, AZD8965 CCI, or AZD8965 CCI for 24 weeks (Week 0 to Week 24).

Follow-up: Participants will have follow-up assessments at CCI CCI after the completion of the treatment period).

Number of Visits for Participants CCI.

- For participants CCI CCI, there are a total of CCI

visits during the study. During the treatment period, visits will occur at [redacted]

- For participants with [redacted] during the treatment period ([redacted]) are required.

Additional Visits (all participants):

- Unscheduled visit(s) may be added to assess potential safety issues as needed during the study.
- For participants permanently discontinuing AZD8965 or placebo early but who are willing to remain in the study, see Section 7.
- Participant who wish to withdraw from the study will be encouraged to complete all the assessments of the Early Termination Visit (unless they do not consent to do so), see SoA Table 1 and Section 7.

The main objective of the study is to evaluate the efficacy and safety of AZD8965 over 24 weeks of dosing. The primary endpoint will be absolute change from baseline in FVC (mL) compared with placebo at Week 24. Secondary assessments include efficacy (absolute change from baseline in FVC percent predicted and rate of decline in FVC), safety and tolerability, and the pharmacokinetics of AZD8965. Pharmacokinetic samples will also be taken from participants who enroll on background antifibrotic therapy as an exploratory assessment at [redacted] to assess whether antifibrotic therapy alters the concentration of AZD8965 and vice versa. [redacted] no exploratory pharmacokinetic samples will be taken for any background antifibrotic therapy.

Sub-studies

This study includes 3 sub-studies.

- HRCT sub-study: details are provided in Section 8.2.2.2.
- PK sub-study (optional for applicable countries): details are provided in Section 8.5.1.3.
- TE sub-study (mandatory for applicable countries): details are provided in Section 8.5.3.

An unblinded IDMC will monitor efficacy and safety, and an URC may be appointed to review the IDMC output. Details will be provided in the IDMC and URC Charters.

A blinded IAC with the expertise to evaluate acute exacerbations of IPF will be appointed. This panel will be comprised of clinical experts in the management of ILDs and/or chest

imaging. Details will be provided in the IAC Charter.

4.2 Scientific Rationale for Study Design

The study will recruit participants globally and aims to detect differentiation between treatment with 3 doses of AZD8965 versus placebo and to select the optimal dose for Phase III studies.

Randomization will be used to minimize bias in the assignment of participants to the treatment arms, to increase the likelihood that known and unknown participant attributes (eg, sex and background therapy) are evenly balanced, and to enhance the validity of statistical comparisons. To reduce potential bias during data collection and evaluation of endpoints, investigator- and participant-blinded treatment will be used during the study. The Sponsor and its agents will also be blinded to the treatment assignment, except for individuals who require access to participants treatment assignments to fulfill their job roles during the clinical trial.

4.2.1 Rationale for Selection of Participant Population

The intended study population is aligned with the intended treatment population (ie, participants with IPF either not on background antifibrotic therapy [either naïve to antifibrotic therapy or those who had previously discontinued antifibrotic therapy at least 12 weeks before Screening] or those who are receiving background antifibrotic therapy [pirfenidone, nintedanib, or nerandomilast], either alone or in combination [Section 6.1.1]). The trial population will include participants with IPF who are 40 years of age or older. Participants who are younger than 40 years of age are not included as they may not be representative of the wider IPF population (Raghu et al 2018).

4.2.2 Rationale for Selection of Primary Endpoint

Change in FVC is a precedented and accepted primary endpoint for clinical trials in IPF. FVC decline likely represents disease progression and is associated with mortality in participants with IPF (Maher et al 2023, Plantier et al 2018). Pirfenidone and nintedanib were approved on the basis of reducing FVC decline, and a numerical trend toward improvement in mortality (hazard ratios < 1) was observed in patients receiving either pirfenidone or nintedanib compared to placebo (Karimi and Chowdhury 2015). More recently, nerandomilast was approved by the FDA based on nerandomilast treatment over 52 weeks significantly reducing FVC decline in participants with IPF (FDA 2025).

4.2.3 Rationale for Number of Doses

Three dose levels are included in this Phase IIb study to ensure robust characterization of the dose-response relationship, in alignment with regulatory guidance. This approach facilitates optimal dose selection for Phase III, balancing efficacy and safety while meeting recommendations for adequate dose-ranging prior to further confirmatory studies.

4.2.4 Rationale for Comparator

The comparator in this study is placebo. Both AZD8965 and placebo may be given in addition to approved antifibrotic therapy. The use of placebo will allow for a double-blind treatment period and an unbiased assessment of the effect of AZD8965.

4.2.5 Rationale for Selection of Study Duration

Multiple analyses from observational cohorts and randomized trials report that decline in FVC over 6 months is associated with increased risk of mortality in IPF (du Bois et al 2011, CCI Zappala et al 2010, Brown et al 2022). The INPULSIS *post hoc* analysis demonstrated that a relative FVC decline > 10% within 6 months predicts subsequent mortality in IPF (Brown et al 2022). These findings support FVC change over 6-months as a clinically meaningful and prognostic endpoint to assess efficacy in studies in IPF. In addition, more recent clinical studies in participants with IPF demonstrated a meaningful separation in FVC trajectories, including in participants on background antifibrotic therapy, over the proposed 6 month study duration (Corte et al 2025, Richeldi et al 2025). Thus, a 6-month study duration is deemed sufficient to detect a treatment effect of AZD8965 on FVC decline.

A 24-week treatment period is also sufficient to identify unfavorable AEs related to new potential IPF therapies and provide an initial assessment of the frequency, severity and reversibility of AEs.

Given that the efficacy and safety profiles of AZD8965 in IPF are not established, limiting the initial exposure to 6 months is appropriate, balancing the need for robust signal detection with minimizing participant exposure to potential risks. This 6-month duration, paired with an appropriately powered sample size, will provide sufficient data to assess early efficacy, characterize safety and tolerability for an initial benefit–risk assessment, and provide the evidence necessary to inform the design of subsequent confirmatory studies.

4.2.6 Patient Input into Design

During protocol development, feedback from patients with IPF was sought via patient engagement panels. The patient engagement panels were led by AstraZeneca and a vendor to seek patient feedback on the AZD8965 clinical study design using interviews. The interviews were conducted on 18 male or female patients with IPF from the USA, Argentina, the United Kingdom, France, Italy, and Japan.

In summary, across all the countries, patients understood the AZD8965 study design and assessments, and they provided positive feedback on the AZD8965 Phase IIb clinical trial.

Specific feedback from the patients on the AZD8965 Phase IIb study included the following:

- The trial length and follow-up period were clear. The 31-week study duration was perceived as appropriate.
- Patients would be willing to attend CCI and a follow-up visit at a local study site.
- Patients were familiar with the different assessments and were willing to perform lung function testing at each visit.
- Some patients would be willing to participate in an HRCT scan sub-study, and others stated that they would likely decline participation in such HRCT scan sub-study.
- Patients were receptive to completing electronic patient questionnaires. Some patients preferred to complete questionnaires at home for time management if possible.
- Safety monitoring during the trial was reassuring to the patients. Patients were interested in understanding the potential benefits and potential risks related to the study and the potential benefits and potential side effects of the study drug.
- Patients were willing to take the study drug as oral tablets CCI

In conclusion, feedback from a global group of patients validated the proposed AZD8965 study design and indicated that they would be receptive to participating in this Phase IIb clinical trial.

The AZD8965 study team also worked with a vendor to understand the IPF patient journey from symptom onset, diagnosis and treatment management. Forty-eight pulmonologists and 30 patients were interviewed from the USA, Argentina, the United Kingdom, France, Italy, and Japan.

Key insights from these interviews included the following:

- Symptoms significantly impact the quality of life of patients with IPF.
- Diagnostic challenges, with primary care physicians not being able to identify IPF symptoms, often lead to late referral or misdiagnosis.
- Treatment that is more effective and durable and has fewer gastrointestinal side effects is desirable.
- For individuals with IPF, there is an unmet need for patient support, patient education and ongoing monitoring that clinical trials provide with additional healthcare professional check-ups.
- Patients with IPF who are most receptive to participating in a clinical trial include those with advanced disease, those with difficulty accessing treatments, and younger patients who desire to continue living a good quality of life.

4.3 Justification for Dose

The AZD8965 CCI CCI AZD8965 treatment for 24 weeks on the primary efficacy endpoint in participants with IPF. CCI CCI CCI CCI CCI The 3 doses selected for this Phase IIb study are AZD8965 CCI AZD8965 CCI and AZD8965 CCI

In a Phase I study in healthy participants (D6960C00001), interim CCI CCI AZD8965 CCI of AZD8965 CCI CCI CCI CCI

4.4 End-of-study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the schedule of activities for the last participant in the study globally.

A participant is considered to have completed the study if they have completed all phases of the study including the last scheduled procedure shown in the SoA.

4.5 Study Stopping Rules

An external IDMC will provide a systematic and unbiased assessment of safety for the study. The IDMC will oversee the safety of the study participants and make appropriate recommendations on further study conduct based on the available data. The IDMC may recommend modification or termination of the study based on regular unblinded safety reviews. Details on the IDMC process and decision criteria will be provided in the IDMC Charter.

If the Sponsor determines that temporary suspension or termination of the study is required, the Sponsor will inform all participating Investigators (or heads of the medical institutions, where applicable) of this decision. When feasible, the Sponsor will provide advance notice to all participating Investigators (or heads of the medical institutions, when applicable) of the impending action. If the study is suspended or terminated for safety reasons, the Sponsor will promptly inform all Investigators, heads of the medical institutions (when applicable), and/or institutions conducting the study. The Sponsor will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution

must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the Sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study. The investigator shall also promptly inform the participant(s) of the study suspension/termination and should ensure the participant(s) receive appropriate therapy and follow-up.

If the AstraZeneca study medical monitor, IDMC or regulatory authorities discover conditions arising during the study that indicate that the participants' safety and/or scientific value of the study and/or quality of the IMP have been compromised, the study will be halted, or the study center's participation will be terminated. Additionally, the Sponsor may determine CCI [redacted], the IDMC would perform this analysis and make a recommendation CCI [redacted] will be defined in an interim analysis SAP and IDMC Charter CCI [redacted]

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all inclusion criteria apply:

Age

1 Participant must be ≥ 40 years at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2 An IPF diagnosis per the 2022 ATS/ERS/JRS/ALAT guideline with central review of a chest HRCT performed within 12 months of Screening confirming a UIP or Probable UIP pattern prior to randomization. Participants with an indeterminate HRCT result are eligible if a prior surgical lung biopsy or transbronchial lung cryobiopsy confirms UIP or Probable UIP histopathology. Participants with an alternative diagnosis HRCT result are eligible if a prior surgical lung biopsy or transbronchial lung cryobiopsy confirms UIP histopathology. All histopathology reports from local reading confirming a diagnosis of IPF must be retained with the participant's source files and the results must be recorded in the eCRF.

3 Participants with IPF receiving locally approved antifibrotic therapies (pirfenidone, nintedanib, or nerandomilast), either alone or in permitted combination (see Section 6.1.1), at a stable dose for at least 12 weeks before Screening and remain on a

stable dose during the Screening period, or participants with IPF not receiving (for any reason) local standard of care (ie, pirfenidone, nintedanib, or nerandomilast) at least 12 weeks before Screening and during the Screening period.

4 FVC ≥ 45% predicted of normal. Re-testing up to 2 times is allowed during Screening if the initial measurements did not meet ATS/ERS/JRS/ALAT criteria for quality and/or reproducibility assessed by central reading.

5 CCI assessed by central reading at CCI CCI CCI at Screening may be re-screened.

6 Forced expiratory volume in one second CCI Re-testing up to 2 times is allowed during Screening if the initial measurements did not meet ATS/ERS/JRS/ALAT criteria for quality and/or reproducibility assessed by central reading.

7 D_{LCO} corrected for hemoglobin ≥ 25% predicted of normal. Re-testing up to 2 times is allowed during Screening if the initial measurements did not meet ATS/ERS/JRS/ALAT criteria for quality and/or reproducibility. A D_{LCO} result corrected for hemoglobin from historical testing within 6 months of Screening is acceptable and does not need to be repeated at Screening.

Sex and Contraceptive/Barrier Requirements

8 Contraceptive use by participants or participant partners should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants:

- Non-sterile males who are sexually active with a WOCBP must use a condom during sexual intercourse from randomization until at least CCI after the last dose of IMP. Male participants are considered non-sterile unless they have previously had bilateral orchidectomy, which should be confirmed by medical assessment and documented in the participant's medical records. Males who have undergone vasectomy, will be considered non-sterile if this procedure is documented in the participant's medical records, and the lack of sperm in the ejaculate is confirmed a minimum of 30 days after the procedure by their physician on two separate occasions separated by a minimum of 30 days.
- The WOCBP partner of a non-sterile male participant must agree to use one highly effective method of contraception, must be stable on their approved contraceptive method for at least 3 months before CCI, throughout the entire duration of the study, and until CCI after the participant has received the last dose of IMP (Table 6).
- Non-sterilized male participants should avoid fathering a child by use of an acceptable form of contraception mentioned in Table 6.

- Complete, sustained abstinence from sexual intercourse with a WOCBP is an acceptable form of contraception, only if this is consistent with the participant's customary lifestyle.

Table 6 Acceptable Methods of Contraception for Female Partners of Childbearing Potential of Non-sterile Male Participants

Type	Method
Non-hormonal	• Bilateral tubal occlusion (caveat: failure rate > 1%) • Intrauterine device (copper) • True sexual abstinence in line with the preferred and usual lifestyle choice of the participant [a] • A vasectomized partner (with confirmed absence of sperm in semen)
Hormonal	• Medroxyprogesterone injection (eg, Depo-Provera®) • Levonorgestrel-releasing intrauterine system (eg, Mirena®) • Etonogestrel-releasing implants (eg, Implanon® or Nexplanon®) • Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Xulane®, Ortho Evra®) • Progesterone based oral contraceptive pill (Cerazette® only)

[a.] Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) are not acceptable.

b) Female participants:

(i) Women who are < 55 years old must fulfill one of the following criteria at Screening to be eligible for the study:

- Be postmenopausal, defined as amenorrhea for ≥ 12 months following cessation of all exogenous hormonal treatments and FSH levels in the postmenopausal range (historical results for FSH will be accepted).
- Have undergone permanent sterilization which includes hysterectomy, bilateral oophorectomy, and bilateral salpingectomy at least 6 weeks before Screening and confirmed by the medical records or follow-up hormone level assessment. Bilateral tubal ligation is not acceptable.
- If they are WOCBP and are sexually active with a potentially fertile male partner, they must be willing to use non-hormonal highly effective contraception measures with low user dependency (Table 7) throughout the study and until 30 days after last dose of IMP. WOCBP participants should be stable on their chosen method of birth control for at least 3 months before the first dose and their male partner must use a condom during sexual intercourse throughout the study.

(ii) Females aged ≥ 55 years must be postmenopausal unless they have undergone sterilization. Postmenopausal is defined as having a ≥ 12 months history of amenorrhea, without an alternative cause, following cessation of all exogenous hormonal treatments.

(iii) Pregnancy testing (for WOCBP only): All WOCBP must have a negative serum pregnancy test result at Screening and a negative urine pregnancy test prior to randomization and IMP administration (see SoA Table 1).

Table 7 Acceptable Methods of Contraception for WOCBP Participants

Type	Method
Non-hormonal	• A vasectomized partner (confirmed absence of sperm in semen) • Bilateral tubal occlusion (caveat: failure rate > 1%) • True sexual abstinence in line with the preferred and usual lifestyle choice of the participant [a] • IUD (copper)

[a.] Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) are not acceptable

Informed Consent

9 Capable of giving signed informed consent as described in Appendix A.

10 Participant is willing and able to:

(a) comply with the requirements of the protocol, including ability to read, write, be fluent in the translated language of all participant-facing questionnaires

(b) attend all study visits and comply with all study procedures.

11 **Optional**: Provision of signed and dated written Optional Genomics Initiative Research Information and Consent Form prior to collection of samples for optional Genomics Initiative research that supports the Genomic Initiative (see Appendix D 2).

12 **Optional**: Provision of signed and dated written HRCT sub-study Consent Form prior to sub-study procedures (if applicable) (see Section 8.2.2.2).

13 **Optional**: Provision of signed and dated written PK sub-study Consent Form prior to sub-study procedures (for participants in applicable countries) (see Section 8.5.1.3).

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions and Diagnostic Assessment

1 ILD other than IPF.

2 The extent of emphysema is greater than the extent of fibrotic changes on chest HRCT scan (determined by central review).

3 Acute exacerbation of IPF within 8 weeks prior to or during Screening. Re-screening is allowed after the participant recovers from the exacerbation per investigator judgment.

4 Lower respiratory tract infection requiring treatment (eg, with antibiotics) within 4 weeks prior to, or during, Screening. Participants may be re-screened after recovering from their infection.

5 CCI [redacted] that may confound assessment of the CCI [redacted] of an arginase inhibitor.

6 QTcF > 450 ms, a known long QT syndrome, high degree II-III atrioventricular (AV) block, sinus node dysfunction with clinically significant sinus pause not treated with a pacemaker, or a ventricular arrhythmia requiring ongoing treatment.

7 Participants with atrial fibrillation/flutter and an inadequately controlled ventricular rate (ie, HR > 100 bpm at rest) or who have not been on stable anticoagulant therapy for at least 8 weeks (unless this therapy is contraindicated). Re-testing the HR up to 2 times is allowed during Screening and if the HR is < 100 bpm on any retest, the participants will be eligible.

8 Acute coronary syndrome/acute myocardial infarction, unstable angina ± coronary intervention with Percutaneous Coronary Intervention or Coronary Artery Bypass Grafting within 6 months prior to or during Screening.

9 Heart failure defined as New York Heart Association (NYHA) Class III or Class IV.

10 History of any clinically important disease or disorder other than IPF which, in the opinion of the PI, may either put the participant at risk because of participation in the study, or influence the results or the participant's ability to participate in the study.

11 Participants with a history of a CCI [redacted] (eg, severe deficiency of CCI [redacted] CCI [redacted], or CCI [redacted]

12 Liver function tests at Screening, defined as:

(a) AST ≥ 2.5 × ULN, or

(b) ALT ≥ 2.5 × ULN, or

(c) TBL ≥ 1.5 × ULN (except for Gilbert syndrome).

Re-testing up to 2 times is allowed during Screening.

13 CCI [redacted]

Re-testing up to 2 times is allowed during Screening.

14 CCI [redacted]

Re-testing up to 2 times is allowed during Screening.

15 CCI [redacted]
CCI [redacted]

16 Known history of allergy to components of the AZD8965 tablet (refer to AZD8965 IB Section 3.2.2).

17 History of organ transplantation or is likely to receive lung transplantation within the next 6 months.

18 Major surgery (in the opinion of the investigator) performed within 6 weeks of randomization or planned during the study period. Participants may be re-screened 6 weeks after surgery or after they have fully recovered from their surgery (whichever is later).

19 New diagnosis/recurrence of malignancy within the past 5 years (except for carcinoma in situ of the uterine cervix, fully resected non-melanoma carcinoma of the skin [eg, basal cell carcinoma, squamous cell carcinoma] with no evidence of recurrence, fully resected ductal carcinoma in situ, fully treated papillary thyroid cancer, and low-risk prostatic cancer under active surveillance).

20 History of relevant viral infections, including any of the following:

(a) HIV infection or receiving anti-viral treatment for HIV or testing positive for HIV at Screening.

(b) Hepatitis A IgM positive at Screening or during Screening. Re-testing is allowed once during Screening (after participant has fully recovered in the opinion of the investigator).

(c) Evidence of active liver disease and/or evidence of chronic liver disease secondary to viral hepatitis during Screening. Any of the following would exclude the participant from the study:

(i) Participants who test positive for hepatitis C antibody, unless HCV RNA levels are undetectable prior to randomization.

- Please note that if the participant has undergone treatment for HCV, then the RNA level must be assessed more than 12 weeks following the end of treatment.

(ii) Participants who test positive for HBV surface antigen.

- Participants with a history of HBV and/or positive HBV core antibody can only enroll if the HBV DNA PCR is negative.
- Participants with a history of HBV vaccination (ie, anti-HBcAb negative) are allowed to enroll.

21 Participants who have active TB or are currently on treatment for active TB.

Other Exclusions

22 Pregnancy or intention to become pregnant during the study, breastfeeding, or unwillingness to use a highly effective method of contraception (refer to inclusion criterion 8) throughout the study in WOCBP or in those who are lactating.

23 Non-sterilized male participants who are sexually active with WOCBP partners who do not agree to use a highly effective method of contraception from the first day of dosing until CCI after the last dose of IMP.

24 Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff, CRO staff, and/or staff at the study site).

25 Active participation in another interventional clinical trial or recent completion of an interventional trial in which the last dose of IMP was administered less than 5 half-lives before Screening.

5.3 Lifestyle Considerations

Participants must abstain from donating blood and plasma from Screening until after the last visit of the study.

5.3.1 Meals and Dietary Restrictions

- All participants CCI must avoid eating CCI before pre-dose sample collection at the CCI. At these visits, the time of the participant's last meal before sample collection will be recorded in the eCRF.
- For participants in the TE sub-study only, participants must avoid eating for CCI before pre-dose sample collection at the CCI visit. At this visit, the time of the participant's last meal before sample collection will be recorded in the eCRF.

5.3.2 Alcohol

- Participants should abstain from alcohol for 24 h before blood sampling at CCI CCI
- Excessive intake of alcohol, defined as > 7 drinks/week for females and > 14 drinks/week for males (where 1 drink = 5 ounces [150 mL] of wine, 12 ounces [360 mL] of beer, or 1.5 ounces [45 mL] of hard liquor), should be avoided during the study.

5.3.3 Activity

- Participants will abstain from strenuous exercise during the 24 h before each blood collection for clinical laboratory tests.

5.3.4 Other Restrictions

5.3.4.1 Reproductive Restrictions

For more detailed reproductive restrictions please refer to Inclusion Criterion 8.

Sperm Donation and Fathering a Child

Participants should not donate sperm or father a child from the time of first IMP dosing until at least CCI after administration of the last dose of IMP.

Ova/Eggs Donation and Participating in ICF

Participants should not donate ova/eggs or participate in IVF from the time of IMP administration until at least 30 days after administration of the last dose of IMP.

5.3.4.2 Restrictions for Antifibrotic Therapy(ies)

For participants not receiving antifibrotic therapy in the 12 weeks before and during Screening, antifibrotic therapies are restricted medications during the full duration of the blinded treatment period. Antifibrotic therapy (eg, initiation of one or more antifibrotic medication), should not be initiated during the 24-week study treatment period, except for disease worsening or for an acute exacerbation of IPF per investigator judgment.

Participants who are on a stable dose of background antifibrotic therapy at and during Screening should plan to remain on this treatment for the duration of the trial. Discontinuation, interruption and/or dose reductions of the background antifibrotic medication are left at the discretion of the investigator (eg, to manage side effects in line with the respective prescribing information). Change in the use of antifibrotic therapy (eg, initiation of a new antifibrotic medication, switching antifibrotic medication, adding another antifibrotic medication on top of antifibrotic therapy, increasing the dose of antifibrotic therapy) is restricted during the full duration of the blinded treatment period, and changes in background antifibrotic medications should not be made, except for disease worsening or for an acute exacerbation of IPF per investigator judgment.

Initiation of new antifibrotic therapies after CCI disease worsening or an acute exacerbation of IPF: the following antifibrotic medications may be initiated or the dose may be changed with the expectation that the participant should continue to take the medication for the duration of the study (unless the medication or combination is not tolerated by the participant):

- Pirfenidone
- Nintedanib
- Nerandomilast
- Nintedanib and nerandomilast (9 mg BID or 18 mg BID)

- Pirfenidone and nerandomilast 18 mg BID

Any changes to use of antifibrotic medications during the blinded treatment period must be recorded in the eCRF. For any changes made to antifibrotic medications, the name and dosage regimen of the antifibrotic medication(s), date(s) of antifibrotic medication administration, and reason for change in antifibrotic medication(s) must be recorded in the eCRF.

5.4 Screen Failures

A screen failure occurs when a screened participant does not meet all eligibility criteria unless otherwise specified in the protocol. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, Informed Consent date, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once, if due to temporary or reversible conditions or due to logistical reasons.

Re-screened participants need to re-consent and will be assigned the same participant number and undergo all Screening assessments again except for CT imaging assessment (if previous scan is acceptable and less than 12 months), D_{LCO} (if previous D_{LCO} is acceptable) and FSH (if previous FSH values are acceptable).

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified medicinal products (classified as IMPs), and other interventions (eg, behavioral) intended to be administered to the study participants during the study conduct.

6.1 Study Intervention(s) Administered

	AZD8965	Placebo
Intervention name	AZD8965	Placebo
Type	Drug	Placebo
Dosage form	CCI tablet	CCI tablet
Unit dose strength(s)	CCI	Not Applicable
Dosage level(s) and regimen	CCI CCI	CCI
Route of administration	Oral CCI	Oral CCI
Use	Experimental	Placebo
IMP or AxMP	IMP	IMP

	AZD8965	Placebo
Sourcing	Provided by AstraZeneca	Provided by AstraZeneca
Packaging and labeling	Study intervention will be provided CCI [redacted] will be labeled as per country requirement.	Study intervention will be provided CCI [redacted] will be labeled as per country requirement.

6.1.1 Permitted Background Antifibrotic Therapies

The permitted background antifibrotic therapies include:

- nintedanib alone,
- pirfenidone alone,
- nerandomilast (9 mg BID or 18 mg BID) alone,
- nintedanib and nerandomilast (9 mg BID or 18 mg BID),
- or pirfenidone and nerandomilast (18 mg BID).

A maximum of CCI [redacted] will be randomized in the study.

6.2 Preparation, Handling, Storage, and Accountability

- The investigator or designee (eg, unblinded pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received at the site and throughout the entire study until authorization is provided for on-site destruction or removal of the IMP, reflecting completion of the study. If a temperature excursion that is outside acceptable limits is detected at any time during the study, sites will follow the reporting procedures provided in Pharmacy Manual; release of IMP for clinical use can only occur once the event has been reviewed and approval is provided by AstraZeneca (or designated party).
- Only participants randomized/assigned to study intervention may receive study intervention, and only authorized site staff may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally-controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, the head of the medical institution (where applicable), or authorized site staff is responsible for IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, final disposition records).

- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3 Assignment to Study Intervention

All participants will be centrally assigned to randomized study intervention using an IRT/RTSM. Before the study is initiated, the log-in information and directions for the RTSM will be provided to each site.

Study intervention will be dispensed at the study visits summarized in SoA.

On Day 1, participants will be assigned a unique number (randomization number) in ascending numerical order at each study site. The randomization number encodes the participant's assignment to one of the 4 arms of the study, according to the randomization schedule generated prior to the study by the Statistics Department at Sponsor/designee. Each participant will be dispensed blinded study intervention, labeled with their unique kit number, throughout the study or until the study is unblinded after data cut-off.

6.3.1 Procedures for Handling Incorrectly Randomized Participants

Participants who fail to meet the inclusion criteria or who meet any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

Where a participant, who does not meet the eligibility criteria, is randomized in error and this is identified before dosing, the participant should be withdrawn from the study. If a participant is withdrawn prior to dosing, they will be replaced.

If a participant, who does not meet the eligibility criteria, but has been randomized or dosed before the error is identified, the investigator should inform the AstraZeneca Study Physician immediately to discuss potential safety concerns and the best interest of the patient and decide whether IMP should be continued or discontinued. The PI will inform the AstraZeneca Study Clinical Lead of the error, and the Sponsor will determine ongoing study recruitment considerations, including whether the participant should be replaced.

6.4 Blinding

Participants and all study site personnel (except selected unblinded site personnel) will be blinded to the treatment assignment during the study. The Sponsor and its agents will also be blinded to the treatment assignment, except for individuals who require access to participant treatment assignments to fulfill their roles during a clinical trial. These roles include, but are not limited to clinical supply chain managers, PK sample handling personnel, IRT/RTSM Service Provider, and the IDMC.

PK samples for the [redacted] AZD8965 should be collected from participants assigned to all treatment arms to maintain blinding of treatment assignment. Laboratories responsible for PK analysis will be unblinded to participant treatment assignments to identify appropriate samples for analysis. PK samples from participants assigned to the placebo arm will not be analyzed for study drug PK concentration unless specifically requested. PK samples for nintedanib, pirfenidone, and/or nerandomilast will be collected in all participants who are taking any of these drugs, including participants randomized to study drug or placebo, [redacted] The IRT/RTSM will provide to the investigator(s) or pharmacist(s) the kit identification number to be assigned to each participant at the dispensing visit.

Routines for this will be described in the IRT/RTSM user manual that will be provided to each center.

The randomization code should not be broken except in medical emergencies when the appropriate management of the participant requires knowledge of the treatment randomization. The investigator documents and reports the action to AstraZeneca, without revealing the intervention assignment given to the participant to the AstraZeneca staff.

AstraZeneca retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to a study intervention and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

The IRT/RTSM will be programmed with blind-breaking instructions. If there is an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the participant's condition, the investigator has the sole responsibility for determining whether unblinding of a participant's intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, AstraZeneca must be notified within 24 h after breaking the blind. The investigator documents and reports the action to AstraZeneca, without revealing the intervention assignment given to the participant to the AstraZeneca staff.

Sponsor safety staff may unblind the intervention assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's intervention assignment, may be sent to Investigators in accordance with local regulations and/or Sponsor policy. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual participant have been made and documented.

6.5 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention(s) under the direction of the investigator or designee. The date, and time if applicable, of dose administered in the clinic will be recorded in the source records and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6 Dose Modification

Not applicable.

6.7 Continued Access to Study Intervention After the End of the Study

There is no continued access to study intervention after the end of the study.

6.8 Treatment of Overdose

For this study, any dose of AZD8965 taken that was greater than the planned doses will be considered an overdose.

There is no known antidote to AZD8965. If there is a known or suspected overdose, symptomatic treatment and monitoring of vital functions should be performed according to routine clinical practice. Immediate discontinuation of the study intervention should be performed, and appropriate symptomatic therapy should be instituted.

In the event of an overdose, the investigator should:

- Instruct the participant to withhold the next 2 doses of AZD8965, evaluate the participant, and consult with the Study Clinical Lead to determine subsequent administration of study intervention.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Refer to Section 8.4.13 for details of AE/SAE reporting related to overdose.
  - Obtain a plasma sample for PK analysis if requested by the Study Clinical Lead (determined on a case-by-case basis).
  - Document the quantity of the excess dose and the duration of the overdose.

6.9 Prior and Concomitant Therapy

Any prior antifibrotic therapies used by the participant, any adverse events or tolerability issues associated with antifibrotic therapies, and reasons for discontinuation of prior antifibrotic therapies must be recorded in the eCRF. Any medication or vaccine (including

over-the-counter or prescription medicines, vitamins, and/or herbal supplements), supplemental oxygen use, CPAP or BiPAP use, or other specific categories of interest that the participant has received in the 12 months before Screening, is receiving at the time of Screening, or receives during the study must be recorded in the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, frequency and route
- Supplemental oxygen flow rate and frequency (eg, continuous, with activity, when sleeping)
- CPAP and BiPAP pressure settings and supplemental oxygen flow rate (if applicable)

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

The list of antifibrotic therapies that are prohibited during the study are shown in Table 8.

Table 8 Prohibited Antifibrotic Therapies

Prohibited Antifibrotic Therapies
Tocilizumab or other anti-IL-6 therapies
Pirfenidone and nintedanib in combination
Pirfenidone and nerandomilast 9 mg BID in combination

6.10 Rescue Medicine

Treatment for acute exacerbation of IPF will be as per local standard of care.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole is handled as part of Appendix A.

7.1 Discontinuation of Study Intervention

Note that discontinuation from study intervention is not the same as a discontinuation or withdrawal from the study (see Section 7.2).

If study intervention is permanently discontinued, the participant should, if possible, remain in the study and complete visits per the SoA. The investigator should instruct the participant to contact the site before or at the time of study intervention is stopped. A participant who decides to discontinue study intervention must always be asked about the reason(s) and the

presence of any AEs. The reason for discontinuation should be documented in the source records and the appropriate section of the eCRF. Participants who have permanently discontinued from further receipt of study intervention will need to be discontinued from the IRT/RTSM. All study intervention should be returned by the participant at their next on-site study visit or unscheduled visit.

For temporary interruptions in IMP administration, refer to Section 7.1.3.

It is highly recommended that the AstraZeneca Study Physician/delegate be consulted before the IMP discontinuation takes place. In case of safety concerns IMP administration must be immediately withheld until the final decision is made.

7.1.1 Permanent Discontinuation of Study Intervention

Reasons for permanent discontinuation of IMP include:

- Participant decision
- Safety reasons (including AEs) as judged by the investigator and/or AstraZeneca where continued treatment may put the participant at undue risk, including but not limited to development of any study-specific criteria for discontinuation, including:
  - Any SAE that is considered related to study intervention by the investigator.
  - Any other AE that, in the opinion of the investigator or the Sponsor, warrants discontinuation of further dosing with the IMP.
  - Any malignancy, except for participants who develop basal cell carcinoma, localized squamous cell carcinoma of the skin, or localized prostate cancer requiring only active surveillance.
  - An anaphylactic reaction.
- Intensive care unit admission with intubation or mechanical ventilation for an IPF-related event
- CCI
  - CCI
    CCI
  - CCI
    CCI
  - CCI
  - CCI
    CCI
    CCI
    CCI AZD8965 CCI

CCI
CCI
CCI
CCI
CCI
CCI

- CCI
  CCI AZD8965 CCI
  at the investigator's discretion these may be performed at a local laboratory). If an individual participant permanently discontinues the study intervention due to CCI criteria, the participant may be evaluated by a CCI at the discretion of the investigator or if it is requested by the Sponsor
- CCI
  CCI
  CCI AZD8965. CCI
  CCI
  CCI
- Pregnancy
  - Treatment should be discontinued immediately, and an AstraZeneca representative notified
- Severe non-compliance with this study protocol
- Lost to follow-up
- Study terminated by the Sponsor

If the IMP is permanently discontinued, the participant should remain in the study to be evaluated for assessments unless consent is withdrawn from further study participation, the participant is lost to follow-up, or the participant elects to enroll in another clinical study. Participants who discontinue IMP and permanently withdraw from the study should come to the clinic for the ETV; see the SoA in Table 1 for data to be collected at/after the time of discontinuation of study intervention and for the evaluations that need to be completed at this visit.

7.1.2 Procedures for Discontinuation of Study Intervention

The investigator should contact the participant if a decision to stop IMP is taken.

The reason for discontinuing treatment and the date of IMP discontinuation decision should be recorded in the source documents and the eCRF. Participants permanently discontinuing IMP administration should be treated locally at the discretion of the investigator.

All participants who prematurely discontinue IMP should return to the site and complete an ETV.

Participants who do not wish to have any follow-up contact will be withdrawn from the study (Section 7.2).

7.1.3 Temporary Discontinuation of Study Intervention and Restarting After Temporary Discontinuation

Reasons for temporary discontinuation of IMP include:

- Development of liver function abnormalities meeting one of the conditions outlined in Appendix F (Hy's Law), or if, in the presence of abnormal liver chemistries, the investigator believes that it is in best interest of the participant to temporarily discontinue the study intervention.
- A clinically significant finding in QTcF (including, but not limited to, changes from baseline in QTcF with the QTcF cut-off > 500 ms or change from baseline over > 60 ms to above > 480 ms confirmed on repeated ECG after approximately 5 minutes) without an alternative etiology. The investigator or qualified designee will determine whether the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Every attempt should be made to maintain participants on the study intervention during the study. If the study intervention has been interrupted, it should be reintroduced as soon as, in the opinion of the investigator, the participant is able to restart study treatment and the participant wishes to resume. No minimum time period is necessary before treatment can resume.

If the participant misses a scheduled visit during the temporary discontinuation of the study intervention, the missed visit should be performed as soon as possible.

The treatment period will not be extended to compensate for the temporary discontinuation.

7.2 Participant Discontinuation/Withdrawal from the Study

The Sponsor has the right to terminate this study or a specific site at any time, which will result in participant discontinuation (see Appendix A 10).

Discontinuation of the participant from the study by the investigator:

- A participant may be discontinued from the study at any time at the discretion of the investigator if continuation is not in the best interest of the participant.

- At the time of discontinuation from the study, the participant must discontinue the study intervention.

Voluntary withdrawal from the study by the participant:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason) without any implication on participant`s rights.
- A participant who wishes to withdraw from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of discontinuation from the study, if possible, an ETV should be conducted, as shown in the SoA.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.
- If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the investigator and the investigator must inform the Local and Global Study Team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and no contact has been established by the time the study is completed.

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

- The site must attempt to contact the participant and re-schedule the missed visit as soon as possible. The participant should be counseled 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, texts, emails, 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 eCRF.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study/been lost to follow-up.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in Section 1.3 SoA. Protocol waivers or exemptions are not allowed.
- Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- All tests during the Screening period: unacceptable tests (eg, due to hemolysis or clotting of blood samples) and laboratory errors are not included in the total counts and, in such instances, must always be re-tested. Re-testing at Screening or for repeat laboratory tests needed for other visits, and additional tests to further evaluate AEs may be performed at a local laboratory.
- Re-testing during the Screening period is not considered re-screening. See Section 5.4 for re-screening details.
- Procedures conducted as part of the participant's routine clinical management (eg, HRCT scan, D_{LCO}, FSH) and obtained before signing of the ICF may be utilized for Screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Instructions for the collection and handling of HBS will be provided in the study-specific Laboratory Manual. Samples should be stored in a secure storage space with adequate

measures to protect confidentiality. For further details on handling of HBS see Appendix C.

- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca or the investigator, as per local health authority/ethics requirements.

8.1 Administrative and Baseline Procedures

Administrative and general/Screening procedures will be performed, which may include:

- Signing the ICF(s)
- Demographics
- Medical and IPF history
- Use of concomitant medications
- Smoking history
- Physical examination
- Height and weight
- ECG
- Vital signs
- Clinical chemistry and hematology
- Viral serology
- FSH (postmenopausal women < 55 years only)
- Serum and urine pregnancy test (for women of childbearing potential only)
- Blood and urine samples (eg, safety, PK analysis, exploratory analyses)
- ePRO
- CCI and urinalysis
- Chest HRCT (if no historical HRCT available as per Section 8.2.2)
- Clinic spirometry
- D_{LCO} corrected for hemoglobin (if no historical D_{LCO} corrected for hemoglobin available, per Section 8.1.2)
- SAEs
- Acute exacerbation of IPF history
- Supplemental oxygen use
- CCI

- CCI
- CCI

8.1.1 Order of Assessments

The proposed order of assessments is designed to ensure that physiological assessments such as heart rate or BP as well as the evaluation of AEs are not accidentally influenced by physical interventions such as a venous puncture. The procedures are recommended to be performed in the following order:

- AEs, AESIs, and SAEs assessment
- Concomitant medication
- History of acute exacerbation of IPF
- History of hospitalization
- 12-lead ECG
- Vital signs (supine BP, pulse, respiratory rate, and body temperature)
- Pulse oximetry measurements
- Height and weight
- Spirometry
- ePRO, including CCI
- CCI
- CCI
- Blood and urine sampling
- SPFQ
- CCI
- CCI
  CCI
- CCI PK sampling (only for all participants enrolled in PK sub-study) (see SoA Table 1)
- HRCT scan (if no historical HRCT available for eligibility or for participants enrolled in HRCT sub-study, as per Section 8.2.2).

8.1.2 D_{LCO}

D_{LCO} must be performed after spirometry if these assessments are performed on the same day.

- For a D_{LCO} measurement performed at Screening, the site will use its own or locally available D_{LCO} equipment. The D_{LCO} value will be corrected for hemoglobin. The site will enter the percent predicted D_{LCO} value corrected for hemoglobin in the eCRF.
- For a historical D_{LCO} measurement corrected for hemoglobin within 6 months of Screening, the site will enter the percent predicted D_{LCO} value corrected for hemoglobin in the eCRF.
- For a historical D_{LCO} measurement without hemoglobin correction within 6 months of Screening, the site will calculate the percent predicted D_{LCO} value corrected for hemoglobin using the hemoglobin value that is closest in time to the date of the historical D_{LCO} test. The site will enter the percent predicted D_{LCO} value corrected for hemoglobin in the eCRF.

For normal predicted D_{LCO} values, different sites may use different formulas, based on the method used to measure D_{LCO} and in compliance with the ATS/ERS guideline on D_{LCO} measurements (Macintyre et al 2005).

D_{LCO} corrected for hemoglobin (Hb) (Hb value must be in g/dL) formula:

Males: D_{LCO} corrected for Hb = Measured $D_{LCO} \times [1.7 \times Hb / (10.22 + Hb)]$

Females: D_{LCO} corrected for Hb = Measured $D_{LCO} \times [1.7 \times Hb / (9.38 + Hb)]$

Percent predicted D_{LCO} corrected for Hb formula:

Percent predicted D_{LCO} corrected for Hb = D_{LCO} corrected for Hb / (Predicted DLCO corrected for Hb) * 100

8.1.3 Unscheduled Visit

There may be situations when a participant requires an unscheduled visit. The investigator must determine which assessments are to be completed based on the reason for the unscheduled visit and the appropriate assessments that are needed to ensure participant safety. Concomitant medications and AEs must be documented at unscheduled visits. All unscheduled visits must be recorded in the eCRF.

8.2 Efficacy Assessments

Planned timepoints for all efficacy assessments are provided in the Section 1.3 SoA.

8.2.1 Clinical Spirometry

Spirometry will be performed to assess lung function parameters including FVC, FEV_1 at study sites in accordance with ATS/ERS 2019 guidelines (Graham et al 2019). At least 3 spirometry maneuvers (from a maximum of 8 attempts) should be achieved on each

occasion that spirometry assessments are performed. Spirometry measurements will be obtained using standardized spirometry equipment provided by a central vendor.

For each study visit, the highest FVC value obtained by a participant with a minimum of three efforts meeting the 2019 ATS/ERS criteria will be recorded as their FVC result. The maximum number of efforts for spirometry measurement by a participant is 8 in one session. The race-neutral Global Lung Function Initiative reference equation will be used to calculate predicted normal values (CCI Bhakta et al 2023).

If a patient fails to meet the study-specified spirometry inclusion or randomization criteria due to technical hardware failure (example: device cannot be calibrated and no measurements are possible, the device is not switching on) or inability to meet quality requirements as per the ATS/ERS 2019 guidelines, they may repeat spirometry at a different point within the time window allotted for that visit. The investigator will be responsible for determining when and if the patient can perform repeat spirometry safely.

8.2.1.1 Spirometry Technique

Spirometry calibration and data quality checks (including monitoring of unexpectedly high variability of results) and details on performing spirometry will be provided in a separate Spirometry Procedures Manual.

The vendor providing central spirometry services will be responsible for assuring that the spirometer used by each site meets ATS/ERS recommendations and that the study site personnel who will be performing the testing are properly trained. It is preferable that the same trained individual performs the PFTs for each participant.

8.2.1.2 Pre-spirometry Restrictions

Participants will be instructed to refrain from vigorous activity and smoking within 1 h of performing spirometry. Participants who use bronchodilator medication will also be instructed to withhold their bronchodilators prior to performing spirometry in accordance with the bronchodilator withholding times noted in Table 9. The time of the most recent bronchodilator usage prior to spirometry will be recorded by the site staff in the eCRF. If the required restrictions have not been adhered to, the investigator should re-schedule the spirometry to the earliest opportunity within the allowed window.

Table 9 Bronchodilators Withholding Times

Bronchodilator medication	Withholding time (hours)
SABA (eg, albuterol, salbutamol)	4-6
SAMA (eg, ipratropium bromide)	12
LABA (eg, formoterol, salmeterol)	24

Bronchodilator medication	Withholding time (hours)
Ultra-LABA (eg, indacaterol, vilanterol, olodaterol)	36
LAMA (eg, tiotropium, umeclidinium, aclidinium, glycopyrronium)	36-48

Dosing with IMP should also be performed after spirometry has been completed.

8.2.1.3 Screening Spirometry

Screening spirometry is essential to inform eligibility and must be repeated if the results are of unacceptable quality grade (see Spirometry Procedures Manual).

Spirometry may be re-tested up to 2 times during Screening if a participant is unable to complete a successful spirometry effort in accordance with ATS/ERS 2019 criteria.

8.2.1.4 Assessment of Spirometry Quality

To ensure the quality of the primary endpoint measurement, spirometry results will be electronically transmitted to a central vendor, and central review of spirometry with over-reading by a central reader blinded to study drug assignment will be implemented. Acceptability of the spirometry data will be determined by the central reader, and sites will document in the eCRF whether or not the spirometry data were acceptable. Only spirometry data that are deemed acceptable by central over-reading will be used for eligibility confirmation and data analysis.

At CCI expedited central over-reading of spirometry data will be used, and the results of central over-reading will be provided to site staff. If spirometry quality is deemed not acceptable by central review, the participant will be re-tested either on the same day (if the maximum number of attempts has not been exceeded) or a subsequent day(s).

Spirometry data from a subset of participants, will also be transferred electronically to an independent, automated over-reading service that will assess quality and concordance with the ATS/ERS guidelines. The results of this automated over-read will not be sent to the clinic and will be used for exploratory analyses.

Further details regarding assessment and processes related to the quality of spirometry will be provided in the Spirometry Procedures Manual.

8.2.1.5 Time of Day for Spirometry

During the study, it is recommended that all post-randomization spirometry assessments should be performed within a window of approximately ± 3 h of the time that the randomization spirometry was performed, if possible.

8.2.1.6 Spirometry Record Keeping

A printed copy of the spirometry report signed and dated by the investigator (or their delegate) must be stored at the study site for source data verification. If a copy cannot be printed, the spirometry measurements (including FVC and FEV_1 values) will be documented in the participant's medical record.

8.2.1.7 Spirometry for Participants who are Hospitalized or Experiencing an Acute Exacerbation of IPF

Participants who are hospitalized for respiratory reasons or experiencing an acute exacerbation of IPF at planned study visits should not perform spirometry assessments for this study. These participants should resume their planned study visits and assessments when they are fit enough to do so. Study-related spirometry assessments can only resume after the participant has fully recovered from the hospitalization or acute exacerbation per investigator judgment.

8.2.2 Chest HRCT Assessment

All obtained HRCT scans within scope of this protocol (historical and on-study) must be submitted in Digital Imaging and Communications in Medicine (DICOM) format to the central imaging vendor. A Radiology Manual, as well as further training by the imaging vendor, will describe details of all HRCT imaging aspects. To conduct an HRCT within the trial, all applicable local regulatory requirements must be satisfied.

8.2.2.1 Central Read for Eligibility

For all participants, the chest HRCT central review will be performed to determine study eligibility during the Screening period. A historical HRCT scan conducted within 12 months of the Screening period may be used to assess eligibility. If a historical chest HRCT scan cannot be provided, or the available scan does not meet the image quality requirements, a prospective HRCT scan will be required during the Screening period. An optimized chest HRCT protocol will be provided to the sites which includes all recommended scan parameters. The prospective HRCT scan should be performed only after other key eligibility criteria have been confirmed and at least 5 business days before CCI to allow sufficient time for sites to receive centralized reading results.

The central read will not constitute a full clinical review. If during the central review process, an unexpected observation is identified and this finding could, in the opinion of the central reviewer, have a significant health consequence, this finding will be shared with the PI. All follow-up testing and final diagnosis will be left to the discretion of the PI, and the costs for any follow-up testing will not be paid or reimbursed by the Sponsor. The PI will be responsible for reporting any AEs identified from incidental findings. Identification of such incidental findings during the central review process should not be expected, and the site maintains responsibility for performing a general clinical review including assessment of all HRCT scan images as per site protocols.

8.2.2.2 HRCT Sub-study

An optional HRCT sub-study will be performed as per SoA (Table 1). Approximately CCI participants in total may enroll in this sub-study. Informed consent will be obtained from participants enrolled in this sub-study using a separate ICF.

Participants will undergo inspiratory chest HRCT scans at CCI : baseline and CCI All HRCT scans should be performed using a standardized protocol provided by the imaging vendor. This ensures optimal image quality for the analysis of study endpoints while minimizing participants' exposure to ionizing radiation, ie, adhering to the ALARA principle. Recommendations for key scan parameters are provided in the separate Radiology Manual for the sub-study.

If a prospective HRCT scan has been performed during Screening for eligibility assessment (details in Section 8.2.2.1), the same scan can be used as the baseline scan in the HRCT sub-study.

If a historical scan is used for eligibility assessment, the baseline HRCT scan should only be performed during the Screening period after the participant has both been confirmed to meet eligibility criteria for the study and has provided separate written informed consent to participate in the sub-study. If a participant met the eligibility criteria based on a historical HRCT scan, but then has a prospective HRCT scan to participate in the HRCT sub-study, the site should confirm the absence of clinically significant findings that would, in the opinion of the investigator, result in the participant being ineligible for the study. A historical HRCT scan performed CCI may be used for the baseline scan, provided the HRCT scan was:

- Acquired with a protocol as specified in the Radiology Manual,
- Confirmed to be of adequate quality for quantitative assessment by the imaging vendor, and
- Performed on the same scanner that is planned to be used for the follow-up HRCT scan.

The follow-up HRCT scan CCI will only be performed on participants in the HRCT sub-study whose baseline HRCT image quality meets quantitative analysis requirement confirmed by the central imaging vendor. This scan may be performed CCI CCI and should be performed using the same scanner and settings as the baseline HRCT scan. If a participant's baseline HRCT is unacceptable, the HRCT scan at CCI will not be performed.

If a participant in the HRCT sub-study experiences a suspected or an adjudicated acute exacerbation of IPF, a radiographically confirmed pneumonia, or a respiratory-related hospitalization during the study or discontinues IMP CCI the HRCT scan CCI

[redacted] will not be performed and the participant will be discontinued from the HRCT sub-study. Participants discontinued from the HRCT sub-study CCI [redacted] in the HRCT sub-study CCI [redacted] of the Phase IIb study.

If a follow-up HRCT scan cannot be obtained, the reason must be recorded in the eCRF.

8.2.3 Assessment of Acute Exacerbations of IPF

An IAC will review the data and adjudicate all potential acute exacerbations of IPF as described in the IAC Charter. Acute exacerbations of IPF are defined as an acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality (Collard et al 2016). Diagnostic criteria are:

- Previous or concurrent diagnosis of IPF,
- Acute worsening or development of dyspnea usually < 1 month in duration,
- CT with new bilateral ground-glass opacity and/or consolidation on a background pattern consistent with usual interstitial pneumonia pattern, and
- Deterioration not fully explained by cardiac failure, fluid overload or infection.

At each study visit, the investigator will ask directed questions to assess whether the participant has experienced an acute exacerbation of IPF since the preceding study visit. For a participant with a clinical presentation that is consistent with an acute exacerbation of IPF, the investigator will review the participant's medical records. If an acute exacerbation of IPF is suspected, spirometry assessments for study visits should not be performed, and a HRCT scan should be performed. All relevant results from clinically indicated testing related to the acute exacerbation of IPF must be collected and entered in the eCRF (eg, medical summary(ies); laboratory, lung function and imaging results; treatment and whether the participant required hospitalization). For details on when a participant who has experienced an acute exacerbation of IPF should resume study visits and study-related spirometry assessments, see Section 8.2.1.7.

8.2.4 Patient Reported Outcomes

ePRO instruments will be completed to assess the treatment benefit and patient experience of AZD8965. Patient reported outcome efficacy data will be collected through use of the following instruments: CCI [redacted]

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

CCI

CCI
CCI
CCI

During clinic visits, it is recommended that the instruments are administered in the order stated in Section 8.1.1. However, if not feasible, ePROs assignment can be completed at any time during the clinic visit.

During clinic visits, instruments are recommended to be administered in the following order:

- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI
- CCI

During clinic visits, the ePRO assessments will be performed at the times indicated in the SoA (Table 1).

Participants will complete all ePRO assessments using an electronic device (eg, handheld or tablet device), which will be associated with a website system. The ePRO assessments must be completed by the participant, without content input from other persons (eg, spouse, family members, or friends). However, the participant may receive assistance from their caregiver or site personnel if they experience difficulties holding the device or entering the data. The electronic device will be the only accepted source of ePRO data.

Patient reported outcome assessments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be

pre-programmed to enable the appropriate assessment to be carried out in the correct order at each specified time point. The electronic device and instructions for completing the assessments electronically will be provided by the site personnel. The data will be transmitted to a centralized database maintained by the electronic device vendor.

The data will be available for access by appropriate study personnel.

The site personnel will ensure that participants are properly trained on the use of this device.

8.2.5 Supplemental Oxygen Use

Supplemental oxygen use (including oxygen flow rate) at rest, when sleeping, or with activity will be recorded via the concomitant medication list. For participants not using supplemental oxygen at randomization and who start using oxygen during the study, the date of supplemental oxygen initiation will be documented in the eCRF.

8.2.6 Assessment of Respiratory-related Hospitalizations

The investigator will ask directed questions and review the participant's file to assess whether the participant had hospitalizations for respiratory-related reasons. This assessment will be performed at the timepoints provided in the SoA (Table 1). All relevant data (eg, relevant medical summary; laboratory, lung function and imaging results; treatment; duration of hospitalization) relating to respiratory-related hospitalization must be collected and recorded in the eCRF.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the Section 1.3 SoA (Table 1).

8.3.1 Physical Examinations

- A complete physical examination will be performed and include assessments of the following; general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), CCI
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Height (without shoes) (Screening Visit only) and weight will be measured and recorded at the time points specified in the SoA (Table 1).

8.3.2 Vital Signs

Vital signs will be measured as specified in the SoA (Table 1).

Vital signs must be taken prior to IMP administration, and before blood drawing and before

spirometry.

- Body temperature, HR, respiratory rate, and blood pressure will be assessed.
- BP and pulse measurements must be preceded by ≥ 5 minutes of rest for the participant in a quiet setting without distractions.

Additional BP measurements can be done at the investigator's discretion.

8.3.3 Electrocardiograms

Twelve-lead ECG will be performed at timepoints as specified in the Section 1.3 SoA (Table 1).

- Triplicate 12-lead ECG(s) will be obtained as outlined in the SoA (Table 1) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals. Collected ECGs are evaluated by the investigator and reported in the eCRF as normal, abnormal but not clinically significant, or abnormal and clinically significant.
- At each timepoint at which triplicate ECGs are required, 3 individual ECG tracings should be obtained as closely as possible in succession, but no more than 2 minutes apart.

8.3.4 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, hematology, viral serology, serum/urine pregnancy testing, and urinalysis will be taken at the visits indicated in the SoA (Table 1).

Additional safety samples or repeat safety samples may be collected if clinically indicated at the discretion of the investigator and these may be performed at a local laboratory. The date, time of collection and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The clinical chemistry, hematology, and urinalysis samples collected at site visits will be performed at a central laboratory. Sample tubes and sample sizes will be described in the Laboratory Manual.

The following laboratory variables will be measured (see Table 10).

Table 10 Laboratory Safety Variables

Hematology [a]	
Basophils (percentage and absolute count)	Monocytes (percentage and absolute count)
Eosinophils (percentage and absolute count)	Neutrophils (percentage and absolute count)
Hematocrit	Platelet count
Hemoglobin	Red blood cell count
Lymphocytes (percentage and absolute count)	Red blood cell distribution width
Mean corpuscular hemoglobin	Reticulocytes absolute count
Mean corpuscular hemoglobin concentration	White blood cell count
Mean corpuscular volume	
Clinical Chemistry	
Alanine aminotransferase	Phosphate
Albumin	Potassium
Alkaline phosphatase	CCI
Aspartate aminotransferase	CCI
CCI	Sodium
Calcium	CCI
Chloride	Thyroid stimulating hormone (Screening Visit only)
Cholesterol	Total bilirubin
Creatine Phosphokinase	CCI
CCI	CCI
CCI	CCI
Free Thyroxine (Screening Visit only)	Triglycerides
FSH levels to confirm postmenopausal state [b]	Unconjugated bilirubin
Gamma glutamyl transferase	CCI
Glucose (fasting)	CCI
CCI	Lactate dehydrogenase
Urinalysis	
CCI	CCI CCI
Viral Serology [d]	
Hepatitis B core antibody total	Hepatitis C virus antibody
Hepatitis A IgM only	HIV (Types 1 and 2) antibodies
Hepatitis B surface antigen	

Pregnancy Testing	
Serum human beta chorionic gonadotrophin for WOCBP at screening	Urine pregnancy test for WOCBP see SoA in Section 1.3 and Section 8.3.4.1 [c]

a. CCI [redacted] CCI [redacted]
b. For postmenopausal females only at Screening.
c. If pregnancy test is positive at ETV an additional serum pregnancy test will be required.
d. Nucleic Acid Testing (NAT) for HBV and HCV when appropriate (see Section 5.2, Exclusion Criteria 20)

If a participant has an AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN please refer to Appendix F, for further instructions.

8.3.4.1 Home Urine Pregnancy Testing (WOCBP Only)

Urine pregnancy test kits for home testing will be dispensed to participants who are WOCBP during their in-clinic visits at CCI [redacted]. At these visits, sites will provide instructions to WOCBP on use of urine pregnancy test kits and information about virtual visits to report the results of home urine pregnancy testing. If there are missed home pregnancy tests, the site must attempt to contact the participant and re-schedule the missed tests as soon as possible.

At CCI [redacted] home urine pregnancy test will be performed by WOCBP, and the participants must report the results of home urine pregnancy test via virtual visits with the site on the day that they perform the test (Table 11). Sites will record the results of home urine pregnancy testing in eCRF. Participants with a positive home urine pregnancy test will be instructed by their site to withhold IMP dosing while awaiting confirmation of pregnancy, assessed in-clinic via an UV, and a serum pregnancy test will be performed.

Table 11 Schedule for Home Urine Pregnancy Testing

Procedure	Intervention Period			Details in Protocol Section
Weeks	CCI [redacted]			
Study Day				
Visit Window (days)				
Urine pregnancy test at home with virtual visits (WOCBP only)	X	X	X	Table 1 and Section 8.3.4.1

8.3.5 Pulse Oximetry

Pulse oximetry measurements will be performed to evaluate oxygen saturation. Measurements will be collected with a probe, placed on the participant's body (eg, fingertip, earlobe), after the participant has been resting in supine position for at least 10 minutes. If participants are

using supplemental oxygen, then the baseline oximetry should be on their usual oxygen flow and not on ambient air. Results will be recorded as oxygen saturation (percentage of oxygenated hemoglobin).

Pulse oximetry will be performed at the timepoints specified in the SoA (Table 1).

8.3.6 CCI

CCI

AZD8965 CCI

CCI

- CCI
- CCI
- CCI
- CCI
- CCI

8.3.6.1 CCI

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8.3.6.2 CCI

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CCI
CCI

CCI
CCI

8.4 AEs, SAEs, and Other Safety Reporting

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

Participants or, when appropriate, a caregiver or surrogate will notify the investigator or designees of symptoms. These must then be assessed by the investigator and if considered an AE it will be reported by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

AE Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity or changes in intensity
- Whether the AE is serious or not
- Investigator causality rating against the IMP(s) (yes or no)
- Action taken on IMP(s)
- AE caused participant's withdrawal from the study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE description
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication(s)

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

AEs will be collected from the time of the first dose of IMP throughout the treatment period and include the follow-up period.

SAEs will be recorded from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, the investigator shall, without undue delay, report the SAE to AstraZeneca, as described in Section 8.4.10.

8.4.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.4.3 Adverse Events of Special Interest

AESI are events of scientific and medical interest specific to understanding of AZD8965 and may require close monitoring and rapid communication by the PI to AstraZeneca. An AESI may be serious or non-serious.

CCI [redacted]

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

These AESIs are further described in Appendix E. See the IB for AZD8965 for additional information on these potential risks/AESIs.

Participants will undergo safety monitoring during the study for these AESIs as per the SoA (Table 1). If the specific stopping criteria are met discontinuation of study intervention is required by the investigator. Further evaluation of the event and/or supportive therapy will be administered as required.

If any protocol-specific AESIs are considered as SAEs or associated with SAEs, they must be reported according to the timelines specified in Section 8.4.10.

8.4.4 Causality Collection

The investigator must assess causal relationship between IMP and each AE, and answer "yes" or "no" to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the IMP?'

For SAEs, causal relationship should also be assessed for any other concomitant medications and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as "yes".

A guide to the interpretation of the causality question is found in Appendix B.

8.4.5 AEs Based on Examinations and Tests

Deterioration as compared to baseline in protocol mandated laboratory values, vital signs, physical examination should only be reported as AEs if they meet any of the following:

- They fulfill any of the SAE criteria
- They are the reason for discontinuation of the IMP
- They are clinically relevant as judged by the investigator which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP (eg, drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and/or symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia vs low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

For IPF, deterioration in lung function or HRCT findings may reflect disease progression and should not be reported as AE unless associated with unexpected clinical signs or symptoms. Routine laboratory changes (eg, liver enzymes) should be reported if clinically significant and not attributable to underlying disease.

Any new or worsening of a clinically relevant abnormal medical finding at a physical examination compared with the baseline assessment will be reported as an AE unless unequivocally related to the DUS. Please refer to Section 8.4.9.

The results from the protocol mandated laboratory tests and vital signs will be summarized in

the CSR.

8.4.6 AEs Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or reported in response to the open question from the study site staff: 'Have you had any health problems since the previous visit/you were last asked?', or revealed by observation will be collected and recorded in the eCRF.

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.7 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix F for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.4.8 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to the disease for which the IMP is being studied. It may be an increase in the severity of the DUS and/or increases in the symptoms of the disease. The development of an acute exacerbation of IPF should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as AEs during the study unless they meet SAE criteria or lead to discontinuation of the IMP. Hospitalizations or deaths due to AE-IPF will be reported as SAEs.

8.4.9 Disease Under Study

Symptoms of the DUS are those which might be expected to occur as a direct result of IPF which requires the exclusion of other forms of interstitial pneumonia including other idiopathic interstitial pneumonias and ILD associated with environmental exposure, medication, or systemic disease. Events which are unequivocally due to DUS should not be reported as AEs during the study unless they meet SAE criteria or lead to discontinuation of the IMP.

8.4.10 Reporting of SAEs

All SAEs must be reported, whether or not they are considered causally related to the IMP. All SAEs will be recorded in the eCRF during study conduct. After study completion, when EDC is closed and SAE (with suspected causal relationship to the IMP) needs to be reported, a

paper SAE form should be used.

If any SAE occurs during the study, Investigators or other site personnel will inform the appropriate AstraZeneca representatives within one day, ie, immediately but **no later than 24 h** from when he or she becomes aware of it.

The designated AstraZeneca representative will work with the investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety DES within **one calendar day** of initial receipt for fatal and life-threatening events and within **5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 h** from when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated e-mail alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports the SAE via a secure method to the appropriate AstraZeneca representative.

When the EDC is temporarily not accessible, the AstraZeneca Study Representative should confirm that the investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

For further guidance on the definition of an SAE, see Appendix B.

For regulatory reporting requirements for SAEs, see Appendix A 1.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca AZD8965.

8.4.11 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study participant has received any study intervention.

8.4.11.1 Maternal Exposure

If a participant becomes pregnant during the study, study intervention should be discontinued immediately and the pregnancy reported to AstraZeneca.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention

may have interfered with the effectiveness of a contraceptive medication. All pregnancies should be collected and provided to the AstraZeneca Patient Safety DES via PREGREP module in the eCRF. If an AE/SAE is associated with the pregnancy, AE/SAE eCRF modules should also be completed and sent to the AstraZeneca Patient Safety DES. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study. The paper based PREGOUT form should be used to report the outcome of the pregnancy.

If any pregnancy occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives immediately but no later than **24 h** after he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety DES **within one or 5 calendar days** for pregnancies associated with SAEs (see Section 8.4.10) and **within 30 days** for all other pregnancies. The same timelines apply when outcome information is available.

8.4.11.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm during the study and for CCI following the last dose.

Pregnancy of the participant's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital anomaly), occurring from the date of the first dose until CCI after the last dose should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the pregnant partner must be obtained before the Pregnancy Report Form is completed.

8.4.12 Medication Error, Drug Abuse, and Drug Misuse

8.4.12.1 Timelines

Medication error, Drug Abuse and Drug Misuse alone are not AEs/SAEs. All Medication Errors/Drug Abuse/Drug Misuse are to be collected for IMPs and provided to the AstraZeneca Patient Safety DES via the respective Medication Error eCRF module or Drug Abuse/Drug Misuse paper CRF forms. If an AE/SAE is associated with the Medication Error/Drug Abuse/Drug Misuse, the AE/SAE eCRF modules should also be completed and sent to the AstraZeneca Patient Safety DES.

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the

investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 h** from when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety DES within one (initial fatal/life-threatening or follow-up fatal/life-threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE associated with the event of medication error, drug abuse, or misuse (see Section 8.4.10) and within 30 days for all other events.

8.4.12.2 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of medication error can be found in Appendix B 4.

8.4.12.3 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.4.12.4 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP or AstraZeneca AxMP for medicinal purposes outside of the authorized product information, or unauthorized IMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.4.13 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

Overdose alone is not an AE/SAE. All overdoses are collected for IMPs and provided to the AstraZeneca Patient Safety DES via the Overdose eCRF module. If an AE/SAE is associated with the overdose, AE/SAE eCRF modules should also be completed and sent to the AstraZeneca Patient Safety DES. An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP occurs during the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 h** from

when he or she becomes aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety DES **within one** (initial fatal/life-threatening or follow-up fatal/life-threatening) or **5** (other serious initial and follow-up) calendar days if there is an SAE associated with overdose (see Section 8.4.10) and within 30 days for all other overdoses.

8.5 Pharmacokinetics and Target Engagement

PK assessments will include analyses of the CCI AZD8965 concentrations in plasma. Additional PK assessment will include analyses of locally approved antifibrotic therapies (nintedanib, pirfenidone, and/or nerandomilast) concentrations in plasma only in participants who are receiving background antifibrotic therapy(ies) CCI CCI

PK samples for the CCI of AZD8965 from participants receiving placebo will not be analyzed, unless there is a need to confirm that the correct treatment has been given to study patients.

TE will be assessed in plasma by measuring the ex vivo conversion of exogenously added stable, labeled L-arginine to labeled L-ornithine to evaluate the extent to which AZD8965 inhibits arginase activity in the circulation.

A PK sub-study (which includes CCI) and a TE sub-study will be performed in applicable countries and will include approximately CCI participants. CCI AZD8965 CCI CCI

8.5.1 Pharmacokinetic Samples

8.5.1.1 Pharmacokinetic Samples for the CCI of AZD8965 CCI

At CCI , participants will withhold their morning dose of IMP. Pre-dose PK samples for AZD8965 (CCI) will then be collected according to the order of assessments (see Table 2 and Section 8.1.1). Following PK blood collection, participants should take their IMP at the study site CCI

For participants who have a clinic visit after noon, IMP should be taken as normal in the morning CCI a pre-dose PK sample will be collected according to the order of assessments (see Table 2 and Section 8.1.1).

The date and time of the most recent IMP dose and the PK sample collection for AZD8965

CCI must be recorded in the eCRF. The next scheduled IMP dose should be taken CCI CCI

8.5.1.2 Pharmacokinetic Samples for Antifibrotic Drug(s) Taken Pre-dose

At CCI participants CCI will withhold their morning dose(s) of antifibrotic drug(s) and bring the medication(s) to the study site. Separate pre-dose PK samples for each antifibrotic agent taken will be collected according to the order of assessments (see Table 3 and Section 8.1.1). Following PK blood collection, participants should take their antifibrotic drug(s) at the study site—pirfenidone and nintedanib with food, and nerandomilast with or without food.

For participants who have a clinic visit afternoon, the background antifibrotic drug(s) should be taken as normal in the morning (with or without food), a pre-dose PK sample will be collected according to the order of assessments (see Table 2 and Section 8.1.1).

The date and time of the most recent dose and the PK sample collection for each antifibrotic drug must be recorded in the eCRF. Participants will then resume their usual dosing schedule for background antifibrotic therapy:

- For participants taking pirfenidone, the next scheduled dose should be taken as close as possible to 8 h after the on-site dose, or at least more than 4 hours after the on-site dose.
- For participants taking nintedanib, nerandomilast, or a combination of nintedanib and nerandomilast, the next scheduled dose of antifibrotic drug(s) should be taken as close as possible to 12 h after the on-site dose, or at least more than 8 hours after the on-site dose. Participants will then resume their usual background antifibrotic dosing schedule.

8.5.1.3 Pharmacokinetic Sampling in PK Sub-study (in Selected Countries)

For participants in the PK sub-study, additional PK blood samples for AZD8965 CCI CCI after dosing with IMP CCI at the study site at CCI (Table 3). CCI PK sample collections for AZD8965 must be recorded in the eCRF.

For antifibrotic therapy, additional CCI CCI will be collected at CCI CCI —pirfenidone and nintedanib with food, and nerandomilast CCI CCI Table 3). The date and time of the CCI PK sample collections for antifibrotic drug(s) must be recorded in the eCRF.

For participants taking pirfenidone, the next scheduled dose should be taken as close as possible to 8 h after the on-site dose, or at least more than 4 hours after the on-site dose. For participants taking nintedanib, nerandomilast, or a combination of nintedanib and

nerandomilast, the next scheduled dose of antifibrotic drug(s) should be taken as close as possible to 12 h after the on-site dose. Participants will then resume their usual background antifibrotic dosing schedule.

8.5.2 Collection of Samples for Pharmacokinetics

Blood samples will be collected at the time points as specified in the SoA (Table 1). Samples will be collected, labeled, processed, stored and shipped as detailed in the Laboratory Manual.

- Plasma samples for the measurement of concentrations of AZD8965 CCI CCI and of antifibrotic medication(s) will be collected as specified in the SoA.
- Participants enrolled in the PK sub-study are required to CCI prior to pre-dose sampling at CCI the time of the participants' last meal consumption prior to pre-IMP dose sampling at CCI will be documented in the eCRF.
- For participants enrolled in the PK sub-study, CCI CCI will be collected at CCI as specified in the SoA and Table 2.
- Samples may be collected at additional time points during the study if warranted and agreed upon by the investigator and AstraZeneca, eg, for urgent safety reasons.
- Samples collected for analyses of CCI of AZD8965 plasma concentrations may also be used to evaluate PK-, safety- or efficacy-related to concerns arising during or after the study.
- For storage, re-use, and destruction of samples for PK see Appendix C.
- PK samples will be disposed of after the Bioanalytical Report finalization or 6 months after issuance of the draft Bioanalytical Report (whichever is earlier).
- Additional analyses may be conducted on the anonymized, pooled, or individual PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.
- Samples collected CCI will be stored and disposed of according to local laws and regulations. PK samples collected CCI will be destroyed 6 months post Bioanalytical Report finalization.

8.5.3 Collection of Samples for Target Engagement

Blood samples will be collected at the time points specified in the SoA (Table 1). Samples will be collected, labeled, processed, stored and shipped as detailed in the Laboratory Manual.

- Participants enrolled in applicable countries will be enrolled in the TE sub-study. Enrollment in the TE sub-study for participants in the applicable countries is mandatory.

- For participants enrolled in the TE sub-study, CCI CCI dose plasma sample will be analyzed for TE from collections at CCI CCI, as described in the SoA.
  - At CCI TE analysis will be performed on CCI CCI sample only. Therefore, no additional sample collection for TE analysis is required at CCI
  - At CCI a sample collection for TE is required only for participants in the TE sub-study, as described in the SoA.
- Participants enrolled in the TE sub-study are required to CCI prior to pre-IMP dose sampling at CCI. The time of the participants' last meal consumption prior to pre-IMP dose sampling at CCI will be documented in the eCRF.
- For storage, re-use, and destruction of samples for TE see Appendix C.

8.5.4 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Additional analyses may be conducted on the samples to further investigate the presence and/or identity of drug metabolites. Placebo samples will not be analyzed for study drug PK concentration, unless there is a need to confirm that correct treatment has been given to study participants. PK samples for nintedanib, pirfenidone, and/or nerandomilast will be analyzed for all participants who are taking any of these drugs, including participants randomized to any active AZD8965 dose or placebo, CCI

Full details of the analytical method used will be described in Bioanalytical Report.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

Incurred sample reproducibility analysis will be performed alongside the bioanalysis of the test samples. The results from the evaluation will be reported in Bioanalytical Report.

8.6 Pharmacodynamics

Not applicable.

8.7 Optional Genomics Initiative

Collection of optional samples for Genomics Initiative research is also part of this study as specified in the SoA and is subject to participant agreement in the optional Genomics Initiative research information ICF.

Blood sample for DNA and blood derivatives isolation will be collected from participants who have consented to participate in the genomic and multi-omics analysis component of the study. Participation is optional. Participants who do not wish to participate in genomic and multi-omics research may still participate in the study.

See Appendix D for information regarding the Genomics Initiative genomic and multi-omics samples. Details on processes for collection and shipment and destruction of these samples can be found either in the appendixes of this protocol or in the Laboratory Manual.

Samples will be collected, handled, labeled, stored and shipped as detailed in the Laboratory Manual.

No samples will be collected from participants in CCI

8.8 Biomarkers

8.8.1 Mandatory Biomarker Sample Collection

The participant's consent to the use of donated biological samples for exploratory biomarker analyses is mandatory except in CCI countries where transcriptomic analysis is not permitted.

Biological samples (plasma, serum, urine, and whole blood) will be collected and may be analyzed for exploratory biomarkers to assess correlations with disease activity, effects of investigational product, and clinical outcomes. The results of this biomarker research may be reported either in the CSR itself or as an addendum, and/or separately in a scientific report or publication. The results of this biomarker research may be pooled with biomarker data from other studies with the investigational product to generate hypotheses to be tested in future research.

Blood samples for exploratory biomarker analyses will be collected at visits according to the schedule of study procedures (Table 1).

8.8.1.1 Blood Samples

Blood samples (plasma and serum) will be collected to evaluate CCI CCI the ARG-1 CCI CCI

8.8.1.2 CCI

CCI CCI

8.8.1.3 CCI

CCI AZD8965 CCI

CCI
CCI

8.8.1.4 RNA CCI

CCI will be collected according to the SoA (Table 1). CCI CCI will be used for the collection, transport, and storage of CCI, and the CCI (Section 8.8.1.5) may be performed on CCI samples.

8.8.1.5 RNA Transcript Profiling of RNA CCI

CCI will be isolated and purified from CCI (Section 8.8.1.4). CCI CCI CCI ARG-1 pathway, may be quantified. The analysis may retrospectively evaluate CCI CCI CCI

8.8.1.6 Storage, Re-use, and Destruction of Biological Samples

Samples will usually be stored for a maximum of 15 years from the date of LSLV, after which they will be destroyed (Appendix C). Any samples collected from participants CCI will be destroyed or repatriated within one year of CSR.

For storage, re-use, and destruction of biomarker samples see Appendix C.

8.8.2 Optional Biomarker Sample Collection

No optional biomarker collection will occur in this study.

8.9 Immunogenicity Assessments

Not applicable.

8.10 Medical Resource Utilization and Health Economics

Not applicable.

8.11 Study Participant Feedback Questionnaire

This study will include an option for participants to complete a questionnaire, the SPFQ, which will give participants the opportunity to provide feedback on their clinical study experience. Participants will be asked to complete the questionnaire in electronic format as indicated in the SoA (Table 1). Individual participant-level responses will be anonymous to the investigator and site staff and so will not be reviewed by the investigator. Coded responses will be used by AstraZeneca to understand participant experience on clinical studies and to

identify where improvements can be made in the clinical study process. To do this, AstraZeneca will combine responses across studies and with data collected as part of the study, such as gender, ethnicity and study duration, to investigate correlations with the participant experience. We may share aggregated data, maintaining individuals' anonymity, with site staff so they can take steps to understand and improve the participant experience at their site. We may also compare the data with responses from other research partners/Sponsors to better understand participant experience in clinical studies across the biopharmaceutical industry. This questionnaire does not collect data about the participant's condition, disease, symptoms, treatment effect, or AEs and therefore would not be considered study data. Consequently, these data do not contribute to any endpoints on the study and will be analyzed and reported separately from the clinical study data. The results of this participant experience analysis may be published or presented at scientific meetings, with AstraZeneca complying with the requirements for publication.

9 STATISTICAL CONSIDERATIONS

The SAP will be signed off by the earliest of the following milestones: 90 days after First Participant In or the first IDMC closed meeting.

The SAP will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

The primary estimand of this study is described in Table 12.

Table 12 Primary Estimand of the Study.

Key Elements	Description
Population	All randomized participants who received ≥ 1 dose of AZD8965 or placebo
Variable	Change from baseline in FVC (mL)
Treatment comparison	Each AZD8965 dose and placebo at 24 weeks
Strategy for intercurrent events:	Three intercurrent events are defined: 1) change in planned treatment (ie, change in planned administration of IMP or change in background therapy); 2) IMP treatment discontinuation; 3) death or lung transplant. The following strategy will be used for intercurrent events (ICH E9 (R1)): • Intercurrent events (except for death or lung transplant) will be handled via a CCI (ie, the occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs). • Intercurrent events of death or lung transplant will be handled via a composite strategy in which ie, their FVC values will be replaced based on CCI in the same treatment CCI
Population-level summary	Mean difference in change from baseline in FVC between AZD8965 and placebo

The primary null hypothesis is that there is no difference between AZD8965 doses and placebo on the change from baseline at Week 24.

The alternative hypothesis is that there is a difference between AZD8965 and placebo on change from baseline in FVC (mL) at Week 24.

This is tested using a CCI at the CCI

In addition, the supportive estimand “While-on-Treatment” will be produced.

9.2 Sample Size Determination

Approximately 360 participants will be randomized into the study, aiming to have approximately CCI evaluable participants at Week 24. Participants will be randomized to placebo, AZD8965 CCI, AZD8965 CCI, or AZD8965 CCI CCI The study, when the sample sizes in the AZD8965 CCI and placebo are CCI will have at least CCI power to detect a difference in means of CCI AZD8965 CCI CCI CCI, and using a CCI with a CCI significance level.

Assuming CCI and a CCI in change from baseline in FVC CCI AZD8965 CCI at Week 24, the study will have at least CCI power to CCI CCI based on the change from baseline in FVC at Week 24.

Table 13 Power calculations for change of baseline in FVC with a sample size of CCI

Endpoint	Clinical important difference (CID) assumed between high dose and placebo	Model	CCI	Power (%) CCI to test dose-response
Primary: Change from baseline in FVC at 24 weeks	CCI			

For CCI , CCI Standard deviation assumed to increase linearly with time from CCI at CCI to CCI at CCI (based on competitor data).

9.3 Populations for Analyses

The following populations are defined:

Table 14 Populations for Analysis

Population/analysis set	Description
Screened	All participants who signed the ICF.
Randomized	All randomized participants.
FAS	All randomized participants who received at least 1 dose of study intervention. Participants will be analyzed according to planned treatment.
SAF	All randomized participants who received at least 1 dose of study intervention and have post-baseline safety data a. Participants will be analyzed according to actual treatment b. Safety analyses will be based on the SAF.
PKS	All randomized participants who received at least one dose of AZD8965 and who have evaluable PK data c for AZD8965, with no important protocol deviations thought to impact the analysis of the PK data. PK data will be reported for the CCI CCI . Participants will be analyzed according to planned treatment. Only PK analyses will be based on the PKS.

a. Post-baseline safety data include at least one among: exposure, adverse events, device events, laboratory data, vital signs, and ECG.

b. If a participant received the study intervention from the wrong kit at least once, the associated actual arm for that participant is the maximum dose actually received.
c. Evaluable PK data for AZD8965 is defined as at least one PK result which may include values below the limit of quantification.

9.4 Statistical Analyses

9.4.1 General Considerations

The primary analysis for the study will be conducted after the last participant has completed the Week 24 visit. AstraZeneca personnel who are directly involved with the conduct of the study, study site personnel, as well as participants will remain blinded to the treatment assignment for individual participants until the completion of the study. Details on what roles will remain blinded and how trial integrity will be maintained will be documented separately.

Unless otherwise defined, the baseline for efficacy variables is defined as the last non-missing assessment before the first dose of the study intervention upon randomization. More details will be provided in the SAP.

9.4.2 Efficacy

9.4.2.1 Primary Endpoint(s)

The primary efficacy endpoint is the change from baseline in FVC at Week 24.

Primary analysis

Change from baseline in FVC CCI in the AZD8965 dose group will be compared to that seen in the placebo group using a CCI This model will be used to perform the statistical tests and to estimate the treatment effect CCI and its CCI The response variable in the model will be the change from baseline in FVC. Treatment, visit, gender, CCI , CCI and treatment by visit interaction will be included as factors in this model. Baseline FVC and CCI will also be included in the model as continuous linear covariates.

CCI will be assumed to model the relationship between pairs of response variables taken at different visits on the same participant. To allow for the possibility that the CCI fails to converge with CCI , the following hierarchical approach is proposed to select a simpler covariance structure if the preceding covariance structure fails to converge: CCI
CCI
CCI

CCI to estimating the degrees of freedom will be used for tests of fixed effects derived from the CCI

Adjusted means from the CCI above will be displayed graphically over

time. Adjusted means will be calculated from the CCI using the CCI CCI in which CCI CCI These analyses use a CCI CCI for those participants who are alive or do not have a lung transplant and will therefore include all available data after treatment discontinuation or change in treatment until the end of the planned treatment period for these participants. For participants CCI CCI will be used and therefore their FVC values will be replaced based on CCI CCI CCI Additional analyses will also be produced for a CCI CCI More details will be provided in the SAP.

Other missing data will be modeled based on what was observed during the study using CCI CCI which is a valid approach under the assumption that data are MAR.

Secondary analyses: CCI
Once estimates from the CCI are derived for each dose, these estimates will then be used to perform the CCI CCI CCI CCI CCI CCI CCI CCI change from baseline in FVC CCI of AZD8965 CCI.

CCI CCI CCI CCI

Descriptive summaries of the primary endpoint will also be presented.

9.4.2.2 Secondary Endpoint(s)

Rate of decline in FVC CCI

The rate of decline in FVC from baseline CCI in the AZD8965 dose groups will be compared to that observed in the placebo group using a CCI. This model will be used to perform the statistical tests and to estimate the treatment effect CCI CCI. The response variable in the model will be the FVC value at each scheduled post-randomization visit CCI. The time effect (measured in weeks) will be added as a continuous covariate into the model. From this time effect, CCI between the FVC, and time is obtained, this

constant represents the change in FVC for unit of time (eg, mL/weeks). The model will include CCI, specifying CCI CCI Additionally, gender, CCI are included in the model, alongside baseline FVC and CCI, which are considered as continuous linear covariates.

These analyses use a CCI for those participants who CCI CCI and will therefore include all available data after treatment discontinuation or change in treatment until the end of the planned treatment period for these participants. For participants CCI, a CCI will be used and therefore their FVC values will be replaced based on CCI CCI CCI

Other missing data will be modeled based on what was observed during the study using CCI CCI which is a valid approach under the assumption that data are MAR.

Additional analyses will also be produced for a supportive estimand: "While-on-Treatment". More details will be provided in the SAP.

Absolute change from baseline in % predicted FVC at Week 24

The absolute change from baseline in % predicted FVC at Week 24 in the AZD8965 dose groups will be compared that in the placebo group using a CCI. The model will be used to perform the statistical test and estimate the treatment effect CCI CCI and its 90% CI. The response variable in the model will be absolute percentage predicted change from baseline in FVC at each scheduled post-randomization visit CCI CCI Treatment, visit, gender, CCI and treatment by visit interaction will be included as factors in this model. Baseline FVC and CCI will also be included in the model as a continuous linear covariate.

Additional analyses will also be produced for a supportive estimand: "While-on-Treatment". More details will be provided in the SAP.

CCI

Once estimates from statistical model are derived for each dose, these estimates will then be used to perform the CCI CCI is used to assess the presence of a dose-response signal using a trend test deducted from a set of pre-specified candidate models. CCI CCI CCI CCI

CCI
CCI
CCI
CCI

Descriptive summaries will also be presented.

9.4.2.3 Exploratory Endpoint(s)

An analysis CCI may also be carried out. More details will be provided in the SAP.

More details about the exploratory analyses will be provided in the SAP.

9.4.3 Safety

Descriptive statistics will be presented for raw values and change from baseline whenever appropriate for all safety endpoints.

All safety analyses will be performed on the safety analysis set.

All AEs will be coded using the most recent version of MedDRA.

AEs (and SAEs separately) will be summarized by study intervention group in incidence summaries by MedDRA system organ class and preferred term. All AEs will be listed and assigned to on/off treatment period.

AEs with an outcome of death, other SAEs/AESIs, and AEs leading to discontinuation will also be summarized separately.

Clinical laboratory safety tests including serum chemistry, hematology, and urinalysis parameters will be summarized using descriptive statistics at each timepoint by treatment group. Change from baseline to each post-baseline timepoint in these data will also be summarized, where appropriate.

Vital signs, pulse oximetry, and clinical laboratory data and ECG will be summarized at each timepoint. Change from baseline to each post-baseline timepoint will also be summarized, where appropriate.

Further details on the analysis of safety data will be described in the SAP.

9.4.4 Pharmacokinetic Analyses

Plasma concentrations of the CCI of AZD8965 will be summarized using descriptive statistics at each visit and timepoint for AZD8965-treated participants. Further details on this will be provided in the SAP.

Additional exploratory PK analyses (including antifibrotic drug(s) plasma concentrations) will be conducted as appropriate and will be reported outside the CSR.

9.4.5 Other Analyses

Subgroup analyses will be performed for CCI categories and for each CCI CCI dding the corresponding treatment by visit by subgroup interaction in the models.

More details about other analyses will be provided in the SAP.

CCI PRO measures, based on blinded data, will be performed in accordance CCI analysis plan and will be reported separately. CCI

9.5 Interim Analysis

The primary analysis will be conducted for this study when all the randomized participants have completed the Week 24 visit.

Additionally, CCI CCI If implemented, the IDMC would CCI CCI and make a recommendation on continuation of the study. CCI guidelines will be defined in an interim analysis SAP and IDMC Charter, if relevant, prior to CCI

9.6 Monitoring/Other Committee

An IDMC will conduct ongoing and periodic unblinded reviews of efficacy, and safety data, with a focus on key potential risks. The IDMC will be responsible for evaluating the cumulative efficacy, and safety data at regular intervals as specified in the IDMC Charter and making appropriate recommendations regarding further study conduct based on the available data. Additional ad hoc IDMC reviews may be requested by the Sponsor. The IDMC will operate independently of all other individuals associated with the conduct of the study, including the study Sponsor.

For details on the IDMC, refer to Appendix A 6 and the IDMC Charter.

An IAC, an independent and blinded expert clinician panel, will be appointed for this study to adjudicate potential acute exacerbations of IPF. The definition of events for independent assessment, criteria for adjudication of events, and details of the adjudication process will be provided in the charter. The clinical panel's composition and a description of its responsibilities will also be provided in the charter. For details on the IAC, refer to Appendix A 6 and the IAC Charter.

An URC may be appointed to review the IDMC output with details provided in an URC

Charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol, applicable laws and regulations, and international standards, including adherence to the relevant ICH GCP Guidelines, which are based on the ethical principles originating from the Declaration of Helsinki.
- Before starting the study at any site, the protocol, IB, ICF, and other relevant documents (eg, advertisements and site-specific materials) must be submitted to and approved by all applicable regulatory authorities and ethics committees, in accordance with local laws and regulations.
- Any revised protocol with changes to the study design must be submitted for approval to the relevant ethics committee(s) and/or regulatory authority(ies) before implementation, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a Service Provider, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research, ISO-14155 for clinical device (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca 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.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- In the EU, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation No 536/2014. All SUSARs to the IMP will be reported to the EudraVigilance database within the required regulatory timelines.

- For all studies except those utilizing medical devices, investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from AstraZeneca will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

A 'Serious Breach' means any deviation of the approved version of the protocol or GCP that is likely to affect the safety, rights of trial participants and/or data reliability and robustness to a significant degree in a clinical trial.

All parties (Sponsor, Service Provider, investigator site staff) involved in the conduct of the clinical trial:

- are responsible for promptly identifying and documenting any actual or potential serious breach.
- should have a process in place to ensure that they are able to identify the occurrence of a (actual/potential) serious breach.
- should report to AstraZeneca (or delegated party) without delay, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca 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 study and for one year after completion of the study.

A 3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study including the risks and benefits, to the participant and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines,

privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be re-consented and if so, this must be to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Participants who are re-screened are required to sign a new ICF.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional HBS. The investigator or authorized designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use, and may withdraw their consent at any time and for any reason during the retention period.

A 4 Recruitment Strategy

Participants are expected to be recruited through clinical chart review, existing participant lists, referrals, advertisement, etc. Details of recruitment strategy and tools will be provided in a separate document

A 5 Data Protection

- Participants will be assigned a unique identifier by Trusted Third Party contracted by the Sponsor or by a PI. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that their personal study-related and coded (pseudonymized) data will be used by AstraZeneca in accordance with local data protection law. The purposes of use and the level of disclosure and use of their data (including the legal basis AstraZeneca relies upon processing their data, where required) must also be explained to the participant in the informed consent.
- The participants must be informed that their medical records may be examined by Quality Assurance auditors or other authorized personnel appointed by AstraZeneca, who are independent of the staff involved in the study in accordance with current Quality Assurance Standard Operating Procedures and Quality Assurance Audit Schedule; by appropriate IRB/IEC members; and by inspectors from regulatory authorities.

- The participant must be informed that data will be collected and used to develop the drug/investigational medicinal product, get permission to introduce and keep it on the market, monitor its safety and get it reimbursed eg, by governments eg, throughout the drug development program, which includes related research activities necessary for this drug development program, including to: understand how the study drug(s) and similar drugs work in the body (eg, evaluate the study drug mode of action, alone or in combination with other study drugs); better understand the studied disease and associated health problems; develop diagnostic tests for the disease; learn from past studies to plan new studies or improve scientific analysis methods; publish research results in scientific journals or use them for educational purposes. AstraZeneca will only collect and use the minimum amount of personal data to support the research and safety monitoring activities within the drug development program and will not make personal data available to anyone (including internal staff) who is not authorized or does not have a business need to know the information.
- The participant must be informed that in some cases their data may be further pseudonymized and/or anonymized.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:
    - Access to the coded data will be restricted and monitored and limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
    - The coded data will be protected with security measures to avoid data alteration, loss, and unauthorized accesses and further de-identification techniques may be applied; as well as other high-standard technical security means such as encryption.
    - A data protection impact assessment (DPIA), where required, will apply to identify and mitigate privacy risks, if any, associated with each scientific research.
    - The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not related to scientific research purposes of the study. In particular, it will not be used to make decisions about future services available to the participant, such as insurance.
- Participants are also protected legally by the following means, if the coded data will be shared with third parties – other companies within the Sponsor group; Service providers; Research partners, who may be located in countries which do not offer the same level of protection as the participants country for which the participant will be informed in the ICF:
    - Within the Sponsor group, the participants' coded data are protected by Binding Corporate Rules. More information about the Sponsor's Binding Corporate Rules are provided here: www.astrazenecabindingcorporaterules.com, or by other contractual arrangements as may be required under local law.

- In all other cases, the participants' coded data is protected by contractual arrangements, Codes of Conduct, or certifications that set the rules for personal data protection to those available in the participant's country or other alternatives set forth in the law, as well as any supplementary technical and organizational measures that may results out of conducted transfer impact assessments, where required.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the Data Controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- While AstraZeneca has processes in place to deal with personal data breaches it is important that Investigators that work with AstraZeneca have controls in place to protect participant data privacy.

The investigator should have a process in place to ensure that:

- allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breaches.
- any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (e-mail address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- have taken all necessary steps to avoid personal data breaches and
- have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards)
- where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach

The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission

- where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions

Notification of personal data breach to participants:

- notification to participants is done by the site for the data breaches that occurred within the processing activities for which the site is the Data Controller and for data breaches occurred within the processing activities of AstraZeneca as the Data Controller, the notification is done in collaboration with the site and is performed by the site and/or PI, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or PI shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.
- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the Data Controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or PI, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca's representative device (ie, Study Monitor laptop), AstraZeneca representative will provide AstraZeneca with all information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the Study Monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the Study Monitor in collaboration with the site and/or PI, acting on behalf of the Sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the Study Monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breaches and performing the mandatory notifications to authorities and participants, where applicable.

A 6 Committees Structure

Independent Data Monitoring Committee

An IDMC will be appointed for this study. The IDMC is a group of independent physicians or scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to AstraZeneca regarding the stopping of a study for lack of efficacy, for harms, CCI . The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study. The IDMC CCI CCI Details about the IDMC will be included in an IDMC Charter.

Independent Adjudication Committee

A blinded IAC with the expertise to evaluate acute exacerbations of IPF will be appointed for this study. This panel will be comprised of clinical experts in the management of ILDs and/or chest imaging. All such events will be adjudicated in a blinded fashion based on available clinical features, laboratory and radiological results.

The IAC and its individual members will follow the processes outlined in the study IAC Charter to reach a consensus result. This approach can be customized in justified instances. Results will be entered into the electronic adjudication system by IAC members.

Unblinded Review Committee

An URC may be appointed to review the IDMC output with details provided in an URC Charter.

A 7 Dissemination of Clinical Study Data

Study overall results, both technical and written in lay language (Trial Results Summary, also known as Lay Language Summary of overall study results), will be submitted to EU Clinical Trials Information System (CTIS) within a year from global End of Trial Date in all participating countries, to ensure scientific integrity, completeness, robustness and reliability of data published results.

A description of this clinical study will be available on www.astrazenecaclinicaltrials.com http://www.clinicaltrials.gov and https://euclinicaltrials.eu/ as will the summary of the study results when they are available. The clinical study and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 8 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate source records that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source records.
- QTLs will be predefined in the location(s) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Oversight Plan(s).
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, Service Providers).
- Study monitors will perform Source Data Verification for sample of sites, participants and data, which will be selected in a risk-based fashion as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorized site personnel are verifiable from source records.
- Study monitors will perform ongoing Source Data Review as per the Monitoring Plan(s) to confirm that data in source are accurate and complete; 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, ICH GCP, and all applicable regulatory requirements.

- Records, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 9 Source Records

- Source records provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source records are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source records must be consistent with the source records or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source records and its origin can be found in monitoring guidelines.

A 10 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants (first site activated).

Start of recruitment is the first participant consented.

Study/Site Termination

AstraZeneca or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by AstraZeneca or the investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, AstraZeneca's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the Investigators, the IRBs/IECs, the regulatory authorities, and any Service Provider(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to participate at another site to continue the study.

A 11 Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca 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 International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AEs

Any unfavorable medical occurrence in a trial participant administered the investigational product. The AE does not necessarily have a causal relationship with the treatment.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study intervention has been administered.

B 2 Definition of SAEs

An SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

- Results in death.
- Is immediately life-threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may jeopardize the participant or may require medical treatment to prevent one of the outcomes listed above.

AEs for **malignant tumors** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **non-SAE**. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the medicinal product would result in the participant's death. 'Life-threatening' does not mean that had an AE occurred in a more

severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important Medical Event or Medical Treatment

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the participant or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

Important medical events:

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

Intensity Rating Scale:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria

shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the medicinal product.

- Time Course. Exposure to suspect drug. Has the participant received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host, or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

For each SAE, the investigator must promptly document in the eCRF that they have reviewed the SAE and have provided an assessment of causality.

Causal relationship in cases where the DUS has deteriorated due to lack of effect should be classified as 'no reasonable possibility'.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, eg, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which led to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication

- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur because of medication errors.

Drug Abuse

For this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study).
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP for medicinal purposes outside of the authorized product information, or for unauthorized IMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole

- Only half the dose is taken because the study participant feels that he/she is feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each center keeps full traceability of collected HBS from the participants while in storage at the center until shipment or disposal (where appropriate) and records relevant processing and tracking information related to the samples while at the site.

The sample receiver keeps full traceability of the samples while in storage and during use until used, disposed of or until further shipment, and keeps record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca team for the remainder of the sample life cycle.

Unless otherwise stated, all appropriately consented samples will be retained for up to a maximum of 15 years from LSLV.

Samples collected from CCI will be destroyed or repatriated within one year of CSR.

If required, AstraZeneca will ensure that remaining human biological tissue samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Human Biological Samples

If a participant withdraws consent to the use of donated HBS, applicable samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant HBS from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented, and study site is notified.

C 3 International Air Transport Association Guidance Document 62nd Edition

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

IATA (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B, or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.
Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN 3373 and IATA 650

Exempt Substances are substances which do not contain infectious substances, or substances which are unlikely to cause disease in humans or animals, are not subject to these regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging

(https://www.iata.org/contentassets/b08040a138dc4442a4f066e6fb99fe2a/dgr-66-en-pi650.pdf)

- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix D Optional Genomics Initiative Research

D 1 Use/Analysis of DNA, and Blood Derivatives

- AstraZeneca intends to collect and store DNA, and blood derivatives (such as plasma and serum) for genomic, and comprehensive omics characterization research (such as protein, nucleotides and other entities in circulation), which may include metabolomic, proteomic and lipidomic analysis, to explore how genomic, and time point omics variations may affect clinical parameters, risk and prognosis of diseases, and the response to medicinal product.
- This genomic, and multi-omics research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care, and to the discovery of new diagnostics, treatments, or medications. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA and multi-omics analysis from consenting participants.
- This optional genomic, and multi-omics research may consist of the analysis of the structure of the participant's DNA, ie, the entire genome.
- The results of these genetic, and multi-omics analyses may be reported in a separate study summary.
- AstraZeneca will store the DNA, and blood derivative samples in a secure storage space with adequate measures to protect confidentiality.

D 2 Multi-omics Research Plan and Procedures

Selection of Multi-omics Research Population

All participants will be asked to participate in this genomic, and multi-omics research. Participation is voluntary and if a participant declines to participate there will be no penalty or loss of benefit. The participant will not be excluded from any aspect of the main study.

Inclusion Criteria

For inclusion in this genomic, and multi-omics research, participants must fulfill all of the inclusion criteria described in the main body of the protocol and: Provide informed consent for the Genomics Initiative sampling and analyses.

Exclusion Criteria

Exclusion from this genomic, and multi-omics research may be for any of the exclusion criteria specified in the main study or any of the following:

The genetic exclusion criteria below apply to blood and saliva samples.

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection
- Healthy volunteer's samples will not be collected for the Genomics Initiative.

Withdrawal of Consent for Multi-omics Research

- Participants may withdraw from this genomic, and multi-omics research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Section 7.2 of the main protocol.

Collection of Samples for Multi-omics Research

- The blood samples for this genomic, and multi-omics research will be obtained from the participants at CCI at randomization. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding participants who may withdraw due to an AE. If for any reason the samples are not drawn at CCI they may be taken at any visit until the last study visit.
- During this study, only one sample should be collected for each of the analyses listed, ie, One for genetics, and one for multi-omics research.

Coding and Storage of DNA, and Multi-omics Samples

The processes adopted for the coding and storage of samples for genomic, and multi-omics analysis are important to maintain participant confidentiality. Samples will be stored for a maximum of 15 years from the date of last participant last visit, after which they will be destroyed. DNA, and blood derivatives are a finite resource that will be used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

- An additional second code will be assigned to the samples either before or at the time of sample processing, replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca analysis laboratories, or at the designated organization. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organizations working with the DNA, or blood derivatives).
- The link between the participant enrollment/randomization code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organizations. The link will be used to identify the relevant samples for analysis, facilitate correlation of genotypic, or multi-omics results with

clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

- The principles for ethical and regulatory requirements for the study, including this genomics, and multi-omics research component, are outlined in Appendix A.

Informed Consent

- The genomic, and multi-omics component of the Genomics Initiative research, outlined in this appendix, are optional and the participant may participate in other components of the main study without participating in this research. To participate in the genomic, and multi-omics component of the study the participant must sign and date both the Consent Form for the main study and the Optional Genomics Initiative Research Information and Consent Form. Copies of both signed and dated consent forms must be given to the participant and the originals filed at the study center. The PI(s) is responsible for ensuring that consent is given freely, and that the participant understands that they may freely withdraw from the genetic aspect of the study at any time.

Participant Data Protection

- AstraZeneca will not provide individual sequencing, genotype, or multi-omics results to participants, any insurance company, any employer, their family members, or general physician unless required to do so by law. Extra precautions are taken to preserve confidentiality and prevent genomic, and multi-omics data being linked to the identity of the participant. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a participant. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a participant's identity and also have access to his or her genomic data. Regulatory authorities may require access to the relevant files, though the participant's medical information and the genomic files would remain physically separate.

Data Management

- Any genomic, or multi-omics data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyze the samples.
- AstraZeneca and its designated organizations may share summary results (such as genetic differences from groups of individuals with a disease) from this genomics, and multi-omics research with other researchers, such as hospitals, academic organizations, or drug- or health-related companies. This can be done by placing the results in scientific

databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health-related research purposes. Researchers may see summary results, but they will not be able to see individual participant data or any personal identifiers.

- Some or all of the clinical datasets from the main study may be merged with the multi-omics data in a suitable secure environment separate from the clinical database.

Appendix E Adverse Events of Special Interest (AESI)

An AESI is an AE of scientific and medical interest specific to understanding of a study intervention and may require close monitoring and rapid communication to AstraZeneca by the investigator. An AESI may be serious or non-serious. The reporting of AESIs allows ongoing surveillance of these events to characterize and understand them in association with the use of a study intervention.

AESI will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs will be assessed by the investigator for severity, relationship to the study intervention, possible etiologies, and whether the event meets criteria for an SAE and therefore requires immediate notification to AstraZeneca. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported as described in Section 8.4.10.

CCI

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Appendix F Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

F 1 Introduction

This appendix describes the process to be followed to identify and appropriately report potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

Specific guidance on managing liver anomalies can be found in Section 7.1.1 of the protocol.

During the study the investigator should remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, potential Hy's Law criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

The investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

F 2 Definitions

Potential Hy's Law
Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law
Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For potential Hy's Law and Hy's Law the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

F 3 Identification of Potential Hy's Law Cases

To identify cases of potential Hy's Law it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

Central Laboratories Being Used:

When a participant meets any of the potential Hy's Law identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator (also sent to AstraZeneca representative).

The investigator will also remain vigilant for any local laboratory reports where the potential Hy's Law identification criteria are met, where this is the case, the investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory eCRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the investigator will without delay:

- Determine whether the participant meets potential Hy's Law criteria (see Appendix F 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

F 4 Follow-up

F 4.1 Potential Hy's Law Criteria not met

If the participant does not meet potential Hy's Law criteria the investigator will:

- Inform the AstraZeneca representative that the participant has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

F 4.2 Potential Hy's Law Criteria met

If the participant does meet potential Hy's Law criteria the investigator will:

- Determine whether potential Hy's Law criteria were met at any study visit prior to starting study intervention (see Appendix F 6).
- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within one day of potential Hy's Law criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'important medical event' and causality assessment 'yes/related' according to the protocol process for SAE reporting.
- For participants who met potential Hy's Law criteria prior to starting IMP, the investigator is not required to submit a potential Hy's Law SAE unless there is a significant change[#] in the participant's condition.
- The Study Clinical Lead will contact the investigator, to provide guidance, discuss, and agree an approach for the study participant's follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
  - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Clinical Lead. This includes deciding which tests available in the Hy's Law laboratory kit should be used.
  - Complete the 3 Liver eCRF Modules as information becomes available.

A 'significant' change in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Clinical Lead if there is any uncertainty.

F 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this appendix should be followed for all cases where potential Hy's Law

criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the Study Clinical Lead will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date potential Hy's Law criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF
- If the alternative explanation is an AE/SAE: Update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term, causality and seriousness criteria) following the AstraZeneca Standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca Standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the Hy's Law case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provide any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to protocol process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

F 6 Laboratory Tests

Hy's Law Laboratory Kit for Central Laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV HBsAg IgM and IgG anti-HBc HBV DNA [a] IgG anti-HCV HCV RNA [b] IgM anti-HEV HEV RNA
Other viral infections	IgM and IgG anti-CMV IgG anti-HSV, and HSV 1 /2 IgM testing or HSV 1/2 PCR [d] IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin) [c]
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-liver/kidney microsomal Ab (Anti-LKM) Anti-smooth muscle Ab (ASMA)
Metabolic diseases	Alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin [c] Transferrin saturation

a. HBV DNA is only recommended when IgG anti-HBc is positive.
b. HCV RNA is only recommended when IgG anti-HCV is positive or inconclusive.
c. CD-transferrin and transferrin are not available CCI. Study teams should amend this list accordingly.
d. HSV 1/2 IgM testing or HSV 1/2 PCR testing depending on region.

Appendix G CCI

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- CCI 3 doses of AZD8965 (CCI and placebo, CCI
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Simulations

1. Datasets simulated

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CCI change from baseline in FVC at Week 24 CCI
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In each study, CCI participants CCI (placebo, AZD8965 CCI AZD8965 CCI and AZD8965 CCI), with CCI participants in the AZD8965 high dose and placebo, and CCI participants in the AZD8965 CCI in a CCI with clinical visits for FVC at CCI . The change from baseline at Week 24 CCI were then evaluated.

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2. Statistical analyses performed on the simulated datasets.

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Estimates for the change from baseline in FVC at Week 24 CCI
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CCI change from baseline in FVC at Week 24 CCI

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[redacted]

Appendix H CCI

H 1 CCI

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H 2 CCI

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H 3 CCI
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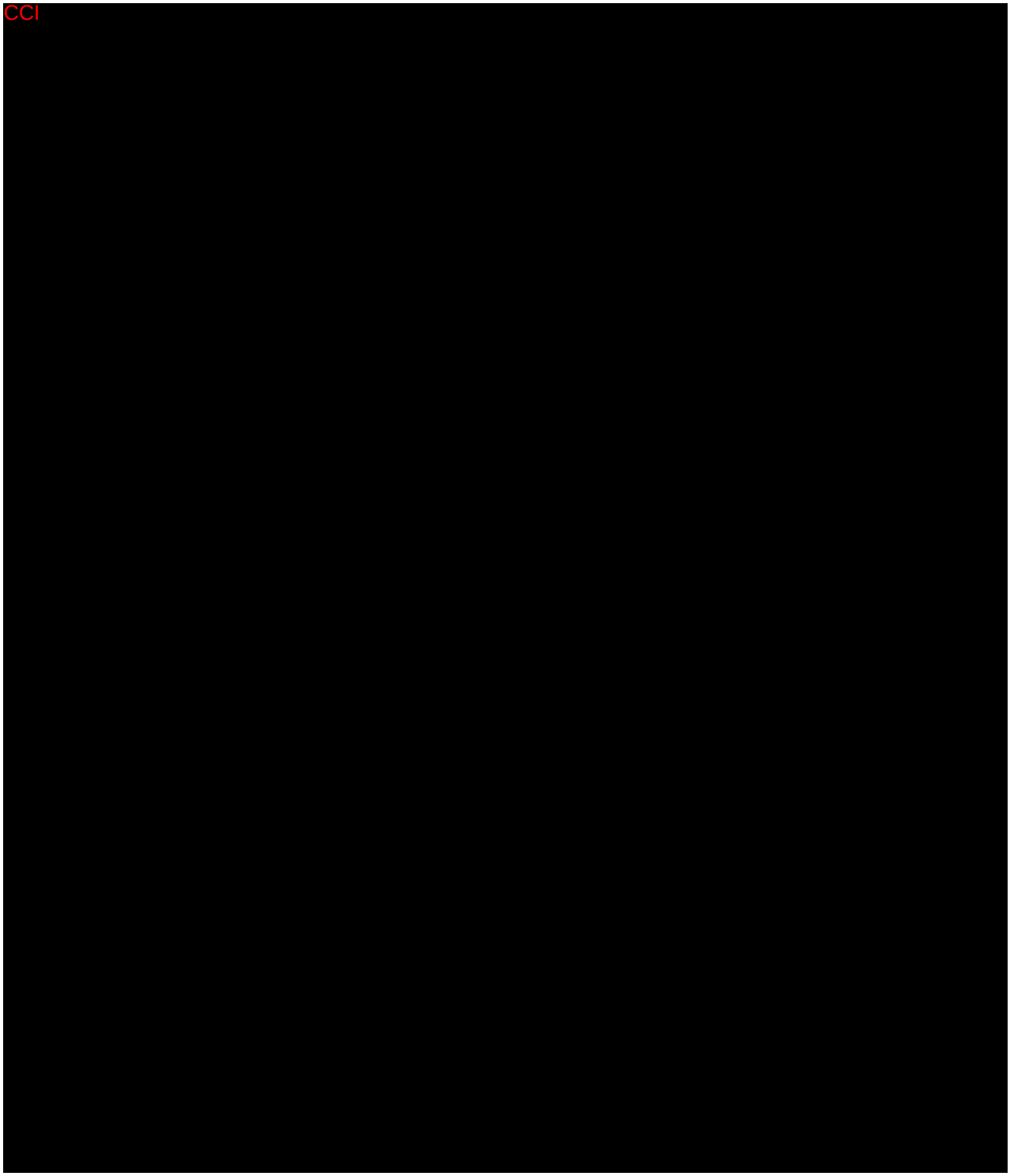
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Appendix I [redacted]

[redacted]

Appendix J CCI

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Appendix K Radiation Safety

All CT scans performed for the purpose of the study should follow the ALARA principle, ie, with radiation doses that are ALARA.

The number of on-study CT procedures/participant/year may range from 0 to 3 depending on CT availability and local radiation exposure regulation limits, instead of 0-1 per year expected as part of clinical routine in IPF population.

To achieve dose optimization, it is necessary to keep the scan length to only the lungs and the tube current (mAs) adjustable for participants of different size and weight. BMI is used to determine mAs settings for each participant scan dependent on body size (small, medium, large).

For sites certified by the imaging vendor that have received an optimized CT instruction form based on the SPIROMICS protocol (Sieren et al 2016) will target the approximate CT dose indices (CTDIvol) values in mGy listed below (reduced dose protocols only applicable for certain CT scanners) (Table K17).

Table K17 Target CT Dose Indices in mGy for CT Protocols Based on SPIROMICS

		Standard Dose Protocols		**Reduced Dose protocols**
Respiratory Phase	Small (BMI < 20)	Medium (BMI 20 - 30)	Large (BMI > 30)	All BMI
Inspiratory scan	6.3 mGy	7.7 mGy	11.4 mGy	< 5.0 mGy

The CTDIvol targets in the table above can be converted to effective dose and site/country-specific derivations may be used. As an example, with medium BMI exposure parameters, a scan length of 30 cm and using an organ weighting coefficient k = 0.027 per AAPM Report 204, these targets correspond to 6.2 mSv at each timepoint.

ICRP 62 radiation risk category will depend on number of on-study scans and scan protocol used (ICRP 1991). The risk is mitigated by the fact that most of the trial population is likely to be > 50 years old where stochastic risks associated with radiation exposure are considerably reduced.

For monitoring purposes, the actual CTDIvol value for each scan should always be provided when uploading the CT images to the vendor. If CTDIvol is not provided, the site should verify that the total radiation risk does not exceed what is stated in the ICF.

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