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VAY736

Clinical Trial Protocol CVAY736X2207

A subject-, investigator-, and sponsor-blinded, randomized, placebo-controlled, multicenter study to investigate efficacy, safety, and tolerability of VAY736 in patients with idiopathic pulmonary fibrosis

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO & PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the Site Operations Manual.

Table of contents

Commercially Confidential Information (CCI)

List of tables

List of figures

List of abbreviations

6MWD	Six Minute Walk Distance
6MWT	Six Minute Walk Test
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AE-IPF	Acute exacerbation of idiopathic pulmonary fibrosis
ALAT	Latin American Thoracic Association
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	Anti-nuclear antibody
ANC	Absolute Neutrophil Count
anti-CCP	Cyclic citrullinated peptide antibody
anti-dsDNA	Double-stranded deoxyribonucleic acid antibody
anti-HBc	Total hepatitis B core antibody
anti-HCV	Hepatitis C antibody
anti-RNP	Ribonucleoprotein antibody
AST	aspartate aminotransferase
ATS	American Thoracic Society
BAFF	B Cell Activating Factor
BAFF-R	B Cell Activating Factor Receptor
BDR	Bioanalytical Data Report
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulation
CHF	Congestive heart failure
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety Commercially Confidential Information
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation

CVA	Cerebrovascular Accident
DAR	Dose Administration Record
DLCO	Diffusing Capacity of the Lungs
DM/PM	Dermatomyositis/polymyositis
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection fraction
ELISA	Enzyme-linked immunosorbent assay
EOS	End of Study
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in first second
FPFV	First patient first visit
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDL	High-density lipoproteins
HIV	human immunodeficiency virus
HRCT	High-resolution computed tomography
i.v.	intravenous
IA	Interim Analysis
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IG	Immunogenicity
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IN	Investigator Notification
INR	International Normalized Ratio
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine system
IVIG	Intravenous immunoglobulin
JRS	Japanese Respiratory Society
LDH	lactate dehydrogenase
LDL	Low-density lipoproteins

mAb	Monoclonal antibodies
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
MI	Myocardial Infarction
mL	milliliter(s)
MOA	Mode of Action
NYHA	New York Heart Association
PBO	Placebo
PD	pharmacodynamic(s)
PFS	Progression Free Survival
PK	pharmacokinetic(s)
PM	Polymyositis
PRO	Patient Reported Outcome
pSS	primary Sjogren's Syndrome
PT	prothrombin time

RA	Rheumatoid arthritis
RF	Rheumatoid factor
RO	Receptor Occupancy
s.c.	subcutaneous
SAE	serious adverse event
Scl	Scleroderma
SD	standard deviation
SGRQ-I	St. George's Respiratory Questionnaire
SLB	Surgical Lung Biopsy
SLE	Systemic lupus erythematosus
SOC	Standard of Care
SOM	Site Operations Manual
SRP	Signal recognition particles
SSA	Sjogren's syndrome-related antigen A
SSB	Sjogren's syndrome-related antigen B
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TBL	total bilirubin
TIA	Transient Ischemic Attack
ULN	upper limit of normal
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of Child Bearing Potential

Pharmacokinetic definitions and symbols

Ctrough	The lowest plasma (or serum or blood) concentration observed during a dosing interval at steady state [mass / volume]
T1/2	The terminal elimination half-life [time]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment, follow-up) which applies across all arms of a study.
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Patient	An individual with the condition of interest
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Screen Failure	A subject who is screened but is not treated or randomized
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy

Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

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Protocol summary

Protocol number	CVAY736X2207
Full Title	A subject-, investigator-, and sponsor-blinded, randomized, placebo-controlled, multicenter study to investigate efficacy, safety, and tolerability of VAY736 in patients with idiopathic pulmonary fibrosis
Brief title	Study of pharmacodynamics, pharmacokinetics, safety and tolerability of VAY736 in patients with idiopathic pulmonary fibrosis
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Biologic
Study type	Interventional
Purpose and rationale	The purpose of this study is to investigate the safety, tolerability and efficacy of VAY736 as potential therapy for the treatment of idiopathic pulmonary fibrosis (IPF).
Primary Objective(s)	To assess the efficacy of VAY736 in patients with IPF by looking at the change from baseline to end-of-treatment (48 weeks of treatment) in forced vital capacity (FVC).
Secondary Objectives	• To assess the impact of VAY736 on safety • To assess the impact of VAY736 on survival • To assess the impact of VAY736 on "progression-free survival (PFS)" • To assess the impact of VAY736 on "disease progression" • To assess the impact of VAY736 on a "Composite Endpoint" • To assess the impact of VAY736 on pulmonary physiology • To assess the impact of VAY736 on exercise capacity • To assess the impact of VAY736 on gas exchange • To assess the immunogenicity of VAY736 in IPF patients • To assess the pharmacokinetics of VAY736 after multiple s.c. doses in IPF patients
Study design	This study will investigate the safety and efficacy of 300 mg VAY736 administered subcutaneously (s.c.) every 4 weeks for 48 weeks. Approximately, 58 subjects will be randomized in a 1:1 ratio on top of local standard of care (SOC), to receive VAY736 or placebo. Randomization will be stratified by SOC treatment (3 levels: nintedanib, pirfenidone, or neither). The population will consist of patients with IPF following ATS/ERS/JRS/ALAT diagnostic guidelines, utilizing HRCT and/or surgical lung biopsy (SLB) as medically indicated. Randomized subjects will participate in a 48 week treatment epoch.

	Commercially Confidential Information This study will utilize an independent, blinded adjudication committee to assess cause of death in case of mortality (IPF- vs. non-IPF-related deaths) and to assess the veracity of diagnoses of acute exacerbations of IPF (Section 10.5). An independent Data Monitoring Committee will periodically review safety data (Section 10.4).
Population	• Male and female subjects 40 to 80 years of age inclusive
Key Inclusion criteria	• A diagnosis of definite or probable IPF within 5 years of the screening visit, as defined by ATS/ERS/JRS/ALAT Diagnostic Guidelines • FVC 40-90% predicted (inclusive) • DLCO, corrected for hemoglobin, 25-79% predicted (inclusive) • FEV1/FVC >70% • Unlikely to die from cause other than IPF within the next 3 years, in the opinion of the investigator • Unlikely to undergo lung transplantation during this trial
Key Exclusion criteria	• Emphysema > fibrosis on screening HRCT (must be confirmed by central reader) • History of major organ, hematopoietic stem cell or bone marrow transplant • Clinically diagnosed AE-IPF or other significant clinical worsening within 3 months of randomization • NYHA class III/IV CHF, EF<25% • Current smoker • Prior use of any B-cell depleting therapy (e.g., rituximab, ofatumumab, or other anti-CD20 mAb, anti-CD40, anti-CD19,anti-CD22 mAb, anti-CD52 mAb, or anti-BAFF mAb)
Study treatment	• VAY736 300 mg s.c. • Placebo s.c.
Pharmacokinetic assessments	• Serum VAY736 concentrations
Efficacy/PD assessments	• Spirometry • DLCO • 6MWT • Oxygen Saturation • B cell count monitoring

Key safety assessments	• Physical Examinations • Monitoring of laboratory markers in blood and urine • ECG • Serious Adverse Events and Adverse Events
Other assessments	Commercially Confidential Information
Data analysis	Change from baseline to end-of-treatment (48 weeks of treatment) in forced vital capacity (FVC) Commercially Confidential Information
Key words	Idiopathic Pulmonary Fibrosis (IPF)

1 Introduction

1.1 Background

Unmet Medical Need

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fibrotic interstitial lung disease, associated with a median survival of 2-5 years from initial diagnosis Raghu et al 2011. IPF affects approximately 1.5 million patients worldwide. Recently, nintedanib and pirfenidone were shown to slow the rate of IPF progression by targeting the biology of fibroblasts King et al 2014, Richeldi et al 2014. However, it was shown that nintedanib and pirfenidone cannot halt the progression of IPF disease. Furthermore, neither nintedanib nor pirfenidone was able to demonstrate a significant impact on IPF mortality. Therefore, a considerable unmet medical need remains.

Rationale for targeting B cells in IPF

There is supporting evidence to suggest that host immune response plays a pivotal role in the pathogenesis of IPF. Immunofluorescent patterns in IPF lung tissue demonstrate the presence of immunoglobulins within the alveolar walls of IPF specimens Schwarz et al 1978. Immune complexes are present in alveolar fluid obtained from patients with IPF Dall'Aglio et al 1988. Transcript analysis demonstrates an increase in expression of immunoglobulin genes in IPF Zuo et al 2002. Tertiary lymphoid tissue (germinal centers and lymphoid aggregates) is present in lung tissue obtained from patients with IPF Marchal-Sommé et al 2006. Radiographic imaging demonstrates the presence of mediastinal and hilar lymphadenopathy in up to 58% of IPF patients Hunninghake et al 2003, Attili et al 2006. Circulating autoantibodies and pulmonary immune complex deposits are seen in a majority of IPF patients Magro et al 2003, Magro et al 2006, Grigolo et al 1998, Fujita et al 1999, Dobashi et al 2000, Ogushi et al 2001, Yang et al 2002, Fischer et al 2006, Takahashi et al 2007, Kurosu et al 2008, Taillé et al 2011. In addition, the presence of autoimmune antibodies in IPF confers a poor prognosis Kahloon et al 2013.

Furthermore, in IPF, B cell abnormalities are common and plasma concentrations of B cell activating factor (BAFF) are elevated Xue et al 2013, drawing a potential link between IPF, abnormal B cells, and autoimmune inflammation. B cell markers, such as CXCL13, are also significantly increased in IPF Vuga et al 2014, DePianto et al 2015. A mechanistic role has been suggested for B cells and BAFF in driving the fibrotic response of the lung François et al 2015, Komura et al 2008.

Taken together, these findings support the idea of specifically targeting B cells to inhibit fibrosis in patients with IPF.

VAY736 is expected to have a durable effect on B cells in the lung

VAY736 is a human monoclonal antibody (mAb) of type IgG1/κ, which specifically binds to the BAFF-receptor (BAFF-R) on B cells.

VAY736 is designed to work by a unique dual mode of action:

1. VAY736 rapidly depletes B cells by triggering antibody-dependent cell-mediated cytotoxicity (ADCC); and
2. VAY736 blocks the BAFF-R on residual B cells in tissue to prevent further activation by rising circulating and local levels of BAFF.

Through this dual mode of action, VAY736 is expected to be more efficacious than either B-cell depletion or BAFF neutralization alone.

1.2 Nonclinical data

1.2.1 Teratogenicity and reproductive toxicity data

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1.3 Clinical data

The pharmacokinetics, safety and tolerability of VAY736 have been evaluated in phase 1 and 2a studies.

1.3.1 Human safety and tolerability data

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1.3.2 Human pharmacokinetic data

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1.3.3 Human pharmacodynamic data

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1.4 Study purpose

The purpose of this study is to investigate the safety, tolerability and efficacy of VAY736 for the treatment of IPF.

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	*Endpoints related to primary objective(s)*
• To assess the efficacy of VAY736 in patients with idiopathic pulmonary fibrosis	• Change from baseline to end of treatment epoch (48 weeks of treatment) in Forced Vital Capacity (FVC).

2.2 Secondary objective(s)

Secondary objective(s)	*Endpoints related to secondary objective(s)*
• To assess the impact of VAY736 on safety	• Adverse Events
• To assess the impact of VAY736 on survival	• a) All-cause mortality b) IPF-related mortality
• To assess the impact of VAY736 on "progression-free survival (PFS)"	• a) Events, defined as: death (all-cause mortality) **OR** "progression" (relative reduction in FVC ≥ 10%) b) Events, defined as: death (IPF-related mortality) **OR** "progression" (relative reduction in FVC ≥ 10%)
• To assess the impact of VAY736 on "disease progression"	• a) Progression, defined as: relative reduction in FVC ≥ 10% b) Progression, defined as: relative reduction in Diffusing Capacity of the Lungs (DLCO) ≥ 15% c) Progression, defined as: absolute reduction in Six Minute Walk Distance (6MWD) ≥ 50 m
• To assess the impact of VAY736 on a "Composite Endpoint"	• a) Events, defined as: death (all-cause mortality), **OR** relative reduction in FVC≥10%, **OR** relative reduction in DLCO ≥15%, **OR** relative reduction in 6MWD ≥50m b) Events, defined as: death (IPF-related morality), **OR** relative reduction in FVC≥10%, **OR** relative reduction in DLCO ≥15%, **OR** relative reduction in 6MWD ≥50m
• To assess the impact of VAY736 on pulmonary physiology	• a) Change from baseline to the end of treatment epoch (48 weeks of treatment) in DLCO

Secondary objective(s)	***Endpoints related to secondary objective(s)***
• To assess the impact of VAY736 on exercise capacity	• a) Change from baseline to the end of treatment epoch (48 weeks of treatment) in 6-minute walk distance b) Change from baseline to the end of treatment epoch (48 weeks of treatment) in distance-saturation product
• To assess the impact of VAY736 on gas exchange	• Change from baseline to the end of treatment epoch (48 weeks of treatment) in resting oxygen saturation (on room air)
• To assess the immunogenicity of VAY736	• Serum anti-VAY736 antibodies
• To assess the pharmacokinetics of VAY736 after multiple s.c. doses	• Serum VAY736 concentrations

2.3 Exploratory objective(s)

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3 Investigational plan

3.1 Study design

This is an exploratory (non-confirmatory) randomized, patient-, investigator-, sponsor- blinded, placebo controlled study of VAY736 in IPF patients. This study will investigate the safety and efficacy of 300 mg VAY736 administered s.c. every 4 weeks for 48 weeks. Approximately 58 subjects will be randomized in a 1:1 ratio on top of local standard of care (SOC), to receive VAY736 or placebo. Randomization will be stratified by SOC treatment (3 levels: nintedanib, pirfenidone, or neither). The randomization scheme will be performed separately within each stratum to ensure balance of the treatment groups with respect to the SOC treatment.

A screening epoch of 6 weeks will be used to assess eligibility. The population will consist of patients with IPF following American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) diagnostic guidelines, utilizing High-Resolution Computed Tomography (HRCT) and/or surgical lung biopsy (SLB) as medically indicated. A central reader (imaging expert) will review the screening HRCT to validate an accurate diagnosis of IPF; and a central reader (pathology expert) will review any prior SLB, if an SLB was necessary for the diagnosis of IPF (i.e., SLB was obtained in the normal course of a diagnostic evaluation). Once eligibility has been assessed during the screening epoch, eligible subjects will be randomized to one of the two treatment arms.

Randomized subjects will participate in a 48 week treatment epoch,

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Please refer to the Assessment Schedule (Table 8-1) for a list of procedures to be performed at each visit. Efficacy assessments will be performed quarterly (Weeks 1, 13, 25, 37, and 49) during the treatment epoch. Safety assessments will be performed at monthly or quarterly intervals during the treatment epoch. HRCT will be performed at screening and again at the end of the treatment epoch.

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Pregnancy tests will be performed monthly in applicable patients during the treatment epoch. This study will utilize an independent, blinded adjudication committee to assess cause of death in case of mortality (IPF- vs. non-IPF-related deaths) and to assess the veracity of diagnoses of acute exacerbations of IPF (Section 10.5). An independent Data Monitoring Committee will

periodically review safety data (Section 10.4).

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Figure 3-1 Study Design

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3.1.1 Rationale of study design

The rationale for key elements of this study are as follows:

- **Placebo controls:** Use of a placebo group is critical to establish the natural history of disease with regard to the endpoints-of-interest (pre-specified primary, secondary, and exploratory endpoints; safety and tolerability endpoints) within the specific population-of-interest and under the specific conditions of this trial. Comparison of endpoints between the active and placebo groups forms the most rigorous test of efficacy. A placebo group also helps to establish a baseline frequency for safety and tolerability events in the population-of-interest, so that safety and tolerability events in the active group may be either attributed to the study drug (if the frequency of events exceeds baseline expectations) or attributed to the underlying disease, concomitant medication, or study procedures (if the frequency of events in the active group is approximately equal to the frequency of events in the placebo group).

(Note: Placebo treatment is an "add-on" to standard-of-care; the investigational treatment is also an "add-on" to standard-of-care.)

- **Randomization/Stratification:** Randomization/Stratification is used to avoid "selection bias" in the assignment of subjects to the treatment groups. Randomization/Stratification also serves to balance the treatment groups with respect to many known and unknown confounding variables; and randomization forms the basis of assumptions for our statistical tests.
- **Subject-, Investigator-, Sponsor blinding:** CCI

  Conscious and unconscious biases are avoided ("detection bias" and "reporting bias", pertaining to outcome assessment) by ensuring that patients, investigators and the Sponsor are unaware of treatment assignment.

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- **Use of central readers for interpretation of diagnostic imaging and lung biopsy specimens:** An element of subjectivity is inherent in the interpretation of radiographic images and lung biopsy specimens. Therefore, in order to create a more homogeneous population for the purposes of this scientific investigation, central readers will be used to standardize these potentially subjective elements of the inclusion/exclusion criteria.
- **Adjudication committee:** To determine cause-of-death and to make the diagnosis of AE-IPF are both difficult tasks, heavily reliant on clinical judgement, and potentially confounded by an element of subjectivity. Therefore, an adjudication committee will be used to standardize the assessment and categorization of these important and clinically meaningful endpoints (IPF-related mortality and incidence of AE-IPF) (Section 10.5).

3.2 Rationale for dose/regimen, route of administration and duration of treatment

The rationale for a 48 week treatment period is as follows:

The purpose of this clinical investigation is to measure the effect of VAY736 on the process of remodeling in the lungs of patients with IPF. However, remodeling is a slow process. A proper investigation of remodeling will require a substantial investment in time in order to reduce the risk of a false negative study due to: **either** (1) no change in the primary endpoint (change from baseline to the completion of the treatment epoch in FVC) at earlier time points; **or** (2) such a small change in the primary endpoint at earlier time points that it is not possible to detect without substantial increase in statistical power (i.e., a substantial increase in the sample size).

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3.3 Rationale for choice of comparator

As described above, VAY736 is added on to SOC, so the best available comparator is placebo added on SOC.

3.4 Rationale for choice of background therapy

Given the serious nature of IPF, it is important that Principal Investigators are allowed to prescribe background therapy that is consistent with the standard-of-care for IPF, as defined in the 2015 ATS/ERS/JRS/ALAT Clinical Practice Guideline Raghu et al 2015. In fact, adherence to the standard-of-care for background therapy is seen as an ethical imperative in the context of such a serious disease.

The 2015 IPF Guideline helps to define the standard-of-care for the treatment of IPF: conditional recommendation is given for the use of nintedanib in patients with IPF; and conditional recommendation is given for the use of pirfenidone in patients with IPF. The guideline provides no recommendation for the use of one treatment over another. Nor does the guideline provide any recommendations for or against the use of combination therapy. Clinicians are advised to individualize treatment decisions by discussing the options with their patients; and clinicians are reminded that many individuals might not want treatment, given uncertainty in the conditional recommendations (uncertainty is due to adverse effects and the high cost of therapy Wilson and Raghu 2015).

In essence, the 2015 IPF Guideline establishes three categories of background standard-of-care treatment for IPF:

1. Treatment with nintedanib alone
2. Treatment with pirfenidone alone
3. No background therapy

3.5 Purpose and timing of interim analyses/design adaptations

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3.6 Risks and benefits

There is no proven direct medical benefit for subjects who will participate in this study. However, a patient's participation in this study will facilitate and advance research in the field of drug development for the treatment of IPF which is still a significant unmet medical need (Section 1.1).

The identified safety risks of BAFF receptor blockade with VAY736 are systemic injection reactions and upper respiratory tract infections.

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The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and compliance with criteria for treatment interruption outlined in the protocol (Section 7.2). Drug-drug interactions are unlikely with biologics, however, sites and patients must strictly observe and adhere to the list of prohibited medications listed in the protocol (Section 5.2).Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

There may be unknown risks of VAY736 which may be serious

3.6.1 Risks of Imaging Procedures

Radiation dose considerations from CT scans – Patients enrolled in this trial will have non-contrast HRCT scans of the lungs at inclusion Commercially Confidential Information
The inclusion scans will consist of two supine scans (one inspiratory and one expiratory) and one prone (inspiratory, if breath-hold is possible in this position), as described in more detail in Section 8.5.3 of this protocol. Commercially Confidential Information

Using validated dose reduction schemes, the effective radiation dose per scan is expected to be as follows: approximately 6 mSv total for inclusion scans and 3 mSv for follow-up. (Breakdown: Inclusion scans- about 3 mSv for the supine inspiratory, 2 mSv for the supine expiratory, and 1 mSv for the prone inspiratory. Commercially Confidential Information

This is considered to be a minor to intermediate risk level corresponding to the benefit to the patient (category IIb based on ICRP62) and is balanced against the possible substantial societal benefit gained from the trial (EC Radiation protection,

1998 and ICR 62, 1992). The radiation dose from CT scans will be in accordance with local clinical practice and regulations.

3.6.2 Blood sample volumes

A maximum of 515 mL of blood is planned to be collected throughout the study, which may last up to three years (one year treatment, with a two year follow-up period). The maximum volume collected at any one visit will not exceed 50 mL. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the SOM. Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and central laboratory manual.

See Section 8.9 regarding the potential use of residual samples.

4 Population

4.1 Inclusion criteria

Those eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female subjects 40 to 80 years of age inclusive
3. A diagnosis of definite or probable IPF within 5 years of the screening visit, as defined by Figure 3, Tables 4-6 of the ATS/ERS/JRS/ALAT Diagnostic Guidelines (Raghu et al 2011, Appendix 3)
5. FVC 40-90% predicted (inclusive)
6. DLCO, corrected for hemoglobin, 25-79% predicted (inclusive)
7. FEV1/FVC >70%
8. Unlikely to die from cause other than IPF within the next 3 years, in the opinion of the investigator
9. Unlikely to undergo lung transplantation during this trial
10. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

4.2 Exclusion criteria

Those fulfilling any of the following criteria are not eligible for inclusion in this study:

1. Emphysema > fibrosis on screening HRCT (must be confirmed by central reader)
2. Active viral, bacterial or other infections requiring systemic treatment at the time of screening or enrollment, or history of recurrent clinically significant infection or of bacterial infections with encapsulated organisms
3. History of major organ, hematopoietic stem cell or bone marrow transplant
4. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes (e.g., mAb of IgG1 class) or to any of the constituents of the study drug (sucrose, L-Arginine hydrochloride, L-histidine, polysorbate 80, hydrochloric acid)
5. Receipt of live/attenuated vaccine within a 2 month period before first dose (V101). (**NOTE:** In accordance with local immunization guidelines, pneumococcal vaccination is recommended for subjects in this trial (based on age and associated risks). Pneumococcal vaccination should be completed at least 4 weeks prior to the first dosing visit. Although, no data exists on the effectiveness of pneumococcal vaccination in patients treated with VAY736, reduced immune responses have been observed after pneumococcal vaccination in patients treated with rituximab (Bingham el al 2010, van Assen et al 2010). Therefore, the Investigator should be aware that pneumococcal vaccination may be less effective in patients treated with VAY736; and the Investigator should exercise judgement (consider risk/benefit) with regards to patients who may require pneumococcal re-vaccination during this study.)
6. History of primary or secondary immunodeficiency, including a positive Human Immunodeficiency Virus (HIV) (Enzyme-linked Immunosorbent Assay (ELISA) and Western blot) test result
7. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin, in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
8. Any one of the following screening values of complete blood count laboratory values: Hemoglobin levels below 8.0 g/dL; Total leukocyte count less than 2,000/µL; Platelets <100.0 x 109/L; Absolute neutrophil count (ANC) <1.5 x 109/L
9. Any surgical, medical (e.g., uncontrolled hypertension, heart failure or diabetes), psychiatric or additional physical condition that the Investigator feels may jeopardize the patient in case of participation in this study
10. Positive hepatitis B surface antigen (HBsAg); or positive total hepatitis B core antibody (anti-HBc); or positive hepatitis C antibody (anti-HCV) unless it can be documented that the patient has received highly-effective HCV-specific antiviral therapy, HCV RNA levels are measured, and HCV RNA is undetectable; (i.e., any acute, latent or chronic infection with hepatitis B or hepatitis C)
11. Evidence of active or latent tuberculosis (TB) infection, as determined by Quantiferon test (after anti-TB treatment, patients with history of or latent TB may become eligible according to national guidelines)

12. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test
13. Clinically diagnosed AE-IPF or other significant clinical worsening within 3 months of randomization
14. Other known causes of interstitial lung disease (e.g., domestic or occupational environmental exposures, drug toxicity) or other identifiable interstitial lung disease
15. Definitive diagnosis of a connective tissue disease (such as systemic sclerosis, DM/PM, RA, Sjogren's syndrome, or SLE)
16. Initiation of pulmonary rehabilitation within 60 days of randomization (i.e., at the time of randomization, patients may continue "maintenance" pulmonary rehabilitation [clinical summary from the Rehabilitation Center must be provided]; new prescriptions for pulmonary rehabilitation are prohibited)
17. Myocardial Infarction (MI), Cerebrovascular Accident (CVA), Transient Ischemic Attack (TIA), or hospitalization for arrhythmia or unstable angina within 6 months
18. New York Heart Association (NYHA) class III/IV Congestive Heart Failure (CHF), Ejection Fraction (EF) <25%
19. Other investigational treatments within 6 months of screening
20. Disability (other than dyspnea) that may limit the completion of 6MWT (angina, claudication, etc.)
21. Current smoker
22. Any current treatment for IPF (except for pirfenidone or nintedanib; but not both)
23. Historical (within 6 months prior to screening) treatment for IPF with experimental or off-label modalities including but not limited to oral corticosteroids, N-Acetylcysteine, cyclophosphamide, mycophenolate, azathioprine, cyclosporine A, etanercept, or plasmapheresis.
    a. Treatment for any indication with any of the following drugs within 6 months prior to screening: oral corticosteroids, N-Acetylcysteine, cyclophosphamide, mycophenolate, azathioprine, cyclosporine A, etanercept, or plasmapheresis. (Note: The aforementioned treatments are systemically distributed and, therefore, might potentially affect the lung regardless of target indication).
24. Prior use of any B-cell depleting therapy (e.g., rituximab, ofatumumab, or other anti-CD20 mAb, anti-CD40, anti-CD19, anti-CD22 mAb, anti-CD52 mAb, or anti-BAFF mAb)
25. Receiving any treatment for pulmonary hypertension OR treatment for pulmonary hypertension anticipated during this trial (in other words, treatment for pulmonary hypertension is prohibited during this trial), including but not limited to epoprostanil, iloprostanil, treprostanil, selexipag, bosentan, ambrisentan, macitentan, sildenafil, tadalafil, and riociguat.
26. History of alcohol and/or drug abuse within the last 2 years
27. Elective surgery planned to take place during this trial

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A total of approximately 58 patients will be enrolled in the study and randomized. If more than 20% of the randomized patients have not completed the 48 weeks of treatment, per protocol, then patients may be replaced.

The investigator must ensure that all subjects being considered for the study meet the above eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of Child Bearing Potential

WOCBP must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirement outlined in the Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

Please refer to Section 4.2 (Exclusion criteria) for details of contraception requirements for the study.

5.2 Prohibited treatment

Use of the treatments displayed in Table 5-1 are NOT allowed during the treatment epoch. Any newly initiated concomitant drug must be individually assessed against the table below to see if it is allowed. If in doubt, the investigator must contact the Novartis medical monitor or designee before allowing a new medication to be started.

Table 5-1 Prohibited Medications

Medication	Prohibited epoch	Action to be taken
Oral corticosteroids (except to treat AE-IPF)	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in electronic Case Report Form (eCRF)
N-acetylcysteine	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF
Azathioprine	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF
Cyclophosphamide	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF
Mycophenolate	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF
Cyclosporine	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF
Colchicine	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF

Medication	Prohibited epoch	Action to be taken
Prostacyclins (epoprostanil, iloprostanil, treprostanil, selexipag)	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF
Endothelin receptor antagonists (ambrisentan, bosentan, macitentan)	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF
PDE5 inhibitors (tadalafil, sildenafil)	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF
Riociguat	Treatment epoch	Discontinue prohibited medication as soon as possible; if not possible, then discontinue study treatment; report in eCRF
Abatacept	Treatment epoch	Discontinue study treatment, report in eCRF
anti-TNF (infliximab, golimumab, certolizumab, adalimumab, etanercept)	Treatment epoch	Discontinue study treatment, report in eCRF
anti-CD19 (blinatumomab)	Treatment epoch	Discontinue study treatment, report in eCRF
Other experimental therapies	Treatment epoch	Discontinue study treatment, report in eCRF
Live/attenuated vaccines	Treatment epoch	Discontinue study treatment, report in eCRF
anti-CD22 (epratuzumab)	Treatment epoch	Discontinue study treatment, report in eCRF
Anti-CD20 (rituximab, ofatumumab, ocrelizumab, veltuzumab)	Treatment epoch	Discontinue study treatment, report in eCRF
Combination therapy with Pirfenidone and nintedanib	Treatment epoch	Discontinue study treatment, report in eCRF
anti-CD52 (alemtuzumab)	Treatment epoch	Discontinue study treatment, report in eCRF

Elective surgery during the treatment epoch is prohibited.

5.3 Dietary restrictions and smoking

Current smokers are excluded at screening, but there are no dietary restrictions for the study.

5.4 Other restrictions

No strenuous physical exercise (e.g. weight training, football) until after Study Completion evaluation. Low intensity exercise (e.g. cycling, walking on a treadmill) is allowed.

6 Treatment

6.1 Study treatment

VAY736 is formulated for s.c. injection. Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM and Pharmacy Manual.

250 mg i.v. methylprednisolone (with or without additional antihistamine and/or paracetamol medication, at the discretion of the investigator) is mandatory prior to the first dose of VAY736. Methylprednisolone will be administered as a 30 minute infusion approximately one hour prior to administration of study treatment.

6.1.1 Investigational treatment and control drug(s)

Vials of VAY736 150 mg and placebo will be supplied by Novartis as open label patient specific kits for at site administration.

6.1.2 Additional study treatment

No additional treatment beyond investigational drug and control drug are included in this trial.

6.2 Treatment arms

Subjects will be assigned to either VAY736 or Placebo treatment arms in a ratio of 1:1. Refer to Section 3.1 and Section 3.2 for information on dosing schedule and rationale.

6.3 Treatment assignment and randomization

Randomization will be stratified by SOC treatment (3 levels: nintedanib, pirfenidone, or no treatment) as these are the only IPF treatments permitted outside of study treatment assignment. Randomized treatment will be assigned to individual subjects by way of a randomization number, Commercially Confidential Information

The randomization number is only used to identify which treatment the subjects have been randomized to receive. The Subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

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The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of subject numbers to

randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers.

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Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

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The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

With the exception of an unblinded pharmacist, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the Treatment

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See Section 7.2 for details on early discontinuation. For detailed information about the scheduled unblinding of subjects, please refer to the SOM.

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

Drug product will be supplied in unblinded subject kits, so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive the treatment allocation from the IRT system. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff

The following unblinded sponsor roles are required for this study:

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All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure until clinical database lock/end of the blinded epochs.

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Table 6-1 Blinding Table

	Time or Event UI: Allowed to be unblinded on individual patient level B: Remains blinded NA: Not applicable to this study			
Role	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	IA
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff	B	UI	UI	UI
Drug Supply and Randomization Group	UI	UI	UI	UI
Unblinded sponsor staff	B	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
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Adjudication Committee	B	B	B	B
All other sponsor staff not identified above (trial team, project team, management & decision boards, support functions)	B	B	UI	UI

6.5 Treating the subject

VAY736 will be administered to the subject via s.c. injection. See the SOM for further details.

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

6.6 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted.

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the Study Team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT at any time (select as applicable) in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- subject number.

In addition, the investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject and, if applicable, whether the subject can continue with follow up assessments.

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with VAY736, as detailed in Section 8.7.

As dosing will be completed within the clinic, assessment of compliance is not applicable.

6.9 Recommended treatment of adverse events

Acute exacerbation of IPF: In the event of an acute exacerbation of IPF, the study drug should be discontinued, pulse-dose corticosteroids may be administered (at the discretion of the Investigator), and the patient should be referred for additional clinical evaluation as appropriate.

Acute injection reactions: First-dose mild-to-moderate injection reactions were observed in the phase 1/2a studies in a substantial subset of patients (see IB). These reactions were anticipated based on mode of action of VAY736, whereby B cell killing leads to release of intracellular cytokines, a mechanism referred to as antibody-dependent cellular cytotoxicity (ADCC). Events reported so far were mainly mild-to-moderate and occurred only after the first

administration of VAY736. However, only very few patients were exposed to multiple doses of VAY736. Reactions included but were not limited to symptoms like chills, headache, fever and nausea, occurred within 24 hours of VAY736 administration and promptly resolved following administration of paracetamol or steroids (e.g., prednisone 50 mg orally).

Reactions are to be considered similar to other B cell depleting antibodies (e.g., rituximab) and can be mitigated by pre-medication. Of note, in the previous studies of VAY736 paracetamol was found to be ineffective to prevent acute injection reactions. By contrast, prednisone 50 mg given orally to a few patients reduced but did not completely prevent these reactions in all premedicated patients (see IB for details). Therefore, for purposes of keeping study personnel and patients blinded and maintain the integrity of the study, a mandatory premedication with i.v. methylprednisolone (with or without additional antihistamine and/or paracetamol medication at the discretion of the investigator) prior to the first VAY736 or placebo dose will be administered in the current trial.

Hypersensitivity reactions: In the event of a hypersensitivity reaction the Investigator should consider the criteria for treatment interruption (Section 7.2) and the patient should be treated with antihistamines and glucocorticoids. Depending on severity, these patients may also require 100% oxygen, volume expansion, catecholamines and transfer to an intensive care setting. Plasmapheresis to decrease the systemic concentration of VAY736 may be considered dependent on the patient's condition. Patients should be observed for at least four hours after resolution of signs and symptoms, and those who have experienced severe infusion reactions should be closely observed for 24 hours after resolution because of the risk for a biphasic episode.

Infections: In the event of an infection, the Investigator should consider the criteria for treatment interruption (Section 7.2), as well as consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof (e.g., antiviral treatment for herpes simplex or zoster) in consultation with infectious disease experts, as appropriate. The Investigator should also consider measuring total serum immunoglobulins and treatment with intravenous immunoglobulin (IVIG), as appropriate.

Vaccinations: It is recommended that, if possible and taking in account the overall status of the patient, potential study participants should complete all pre-planned immunizations in accordance with current immunization guidelines at least 4 weeks prior to VAY736 administration. Live vaccinations should not be given to patients within 2 months of planned exposure to VAY736 or during the period of B cell depletion due to VAY736.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

Use of rescue medication (corticosteroids) are allowed for the treatment of acute exacerbation of IPF, at the discretion of the Investigator, but must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.11 Concomitant treatment

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them.

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All SAEs must be reported as described in Section 9.2 and the SOM. Documentation of attempts to contact the subject should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Discontinuation of study treatment for any individual patient is defined as: when study drug is stopped earlier than planned, as specified in the protocol.

Discontinuation of study treatment can be initiated by either the patient, the investigator, or Novartis.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would negatively impact the risk/benefit of trial participation.

In addition study treatment must be discontinued under any of the following circumstances:

- Patient wish
- Pregnancy
- Patient receives a lung transplantation
- Patient experiences an infection with an opportunistic organism
- Use of a prohibited treatment as outlined in Table 5-1
- Any protocol deviation that results in a significant risk to the subject's safety
- Any situation in which study participation might result in a safety risk to the patient
- Patient having received a live/attenuated vaccine
- Adverse events, abnormal laboratory values, or abnormal test results that indicate a safety risk to the patient (for liver events, refer to Appendix 1; and renal events, refer to Appendix 2).
- Emergence of the following specific adverse event: acute exacerbation of idiopathic pulmonary fibrosis (AE-IPF) as per the International Working Group Report (Collard et al 2016)
- Patient is non-compliant with study treatment, as defined by missing more than one dose

The investigator must contact the IRT to register the subject's discontinuation from study treatment.

Patients that become pregnant during the study should be followed up as per the Assessment schedule. The Investigator may determine whether any assessments should not be performed if, in conjunction with the patient's treating physician/obstetrician, the assessment is considered not to be clinically appropriate.

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If a subject withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's withdrawal from the study and record this information on the eCRF. For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting, in the source documents, the steps that were taken to contact the patient (e.g., dates of telephone calls, registered letters, etc.).

If discontinuation of study treatment occurs, the patient should NOT automatically be considered withdrawn from the study UNLESS they withdraw their consent. As long as the patient has not withdrawn, a patient who has discontinued study treatment should continue to be followed up as per the Assessment schedule.

For patients who discontinue treatment early:

If a patient discontinues treatment early, for whatever reason, the patient is encouraged to complete the protocol scheduled visits to assess safety and spirometry. If the patient opts not to complete the scheduled visits, then clarify whether the patient desires to withdraw.

For patients who desire to withdraw:

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7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as described in Section 7.2 and the Assessment Schedule (Table 8-1).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be formally considered lost to follow-up until his/her scheduled EOS visit would have occurred.

7.5 Study Stopping rules

Study drug considerations: Commercially Confidential Information However, injection/infusion reactions (hypersensitivity, cytokine release, anaphylaxis) can occur with administration of biologics, in particular those biologics which are lymphocyte-depleting by ADCC; and there is an increased susceptibility to infection with any therapy that targets elements of the immune system.

Disease considerations: IPF is a serious and complicated disease with a high rate of IPF-related serious adverse events (~30% in historical populations; Chowdhury 2014) and IPF affects older patients who commonly suffer from additional comorbidities (such as diabetes, chronic obstructive pulmonary disease, coronary artery disease). Therefore, suspected drug-related AEs may be confounded by presentation that is similar to IPF-related AEs or similar to other disease-related AEs.

Thus, unblinded safety reviews will be conducted by an independent and external DMC, on a regularly-scheduled and *ad hoc* basis. In addition, blinded safety data, including events-of-special-interest and disease-specific events, will be evaluated by the Sponsor on a continuous, ongoing basis.

The study can be terminated by the Sponsor at any time for any reason. This may include reasons related to the benefit-risk assessment of participating in the study, for practical reasons (including slow enrollment), discontinuation of study drug development, or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider subject welfare and safety.

But given the seriousness and complexity of IPF, some decisions to stop this study (e.g., related to benefit-risk assessment; related to safety) will be based on recommendations of the DMC.

The following guidance is provided:

- If the DMC concludes that the study drug caused a single SAE where there is reason to conclude that the study drug caused the event (as such, meeting the criteria for being a serious adverse reaction (SAR)) then study enrollment will be paused, and no further dosing will occur, pending a full DMC safety review. If the DMC is concerned about the incidence and/or severity of AEs in the study then study enrollment will be paused pending a full DMC safety review.

Should early termination be necessary, all patients must be seen as soon as possible.

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7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), discontinuation of study drug development, or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider subject welfare and safety. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment schedule

CCI

Epoch	Screening	Treatment[2]														
Visit Name	Screening	Treatment														
Visit Numbers[1]	1	101[13]	103	104	105	106	107	108	109	110	111	112	113	114	115	199
Weeks	-6 to -1	1	5	9	13	17	21	25	29	33	37	41	45	45	49	49
Days	-42 to -1	1	29 ±2	57 ±5	85 ±5	113 ±5	141 ±5	169 ±5	197 ±5	225 ±5	253 ±5	281 ±5	309 ±5	312 ±5	337 ±5	337 ±5
Time (post-dose)	-	-	-	-	-	-	-	-	-	-	-	-	-	72h	-	-
Informed consent	X															
Demography	X															
Alcohol Test, Drug Screen, and Cotinine Test	S															
Hepatitis screen	S															
Tuberculosis test	S															
HIV screen	S															
Pregnancy and assessments of fertility[3]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Body Height and Weight[4]	X														X	
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Body Temperature	X	X			X			X			X				X	
Blood Pressure, Oxygen saturation, and Pulse Rate	X	X			X			X			X				X	
Clinical Chemistry	X	X			X			X			X				X	
Hematology	X	X			X			X			X				X	
Urinalysis	X	X			X			X			X				X	

CCI

Epoch	Screening	Treatment[2]														
Visit Name	Screening	Treatment														
Visit Numbers[1]	1	101[13]	103	104	105	106	107	108	109	110	111	112	113	114	115	199
Weeks	-6 to -1	1	5	9	13	17	21	25	29	33	37	41	45	45	49	49
Days	-42 to -1	1	29 ±2	57 ±5	85 ±5	113 ±5	141 ±5	169 ±5	197 ±5	225 ±5	253 ±5	281 ±5	309 ±5	312 ±5	337 ±5	337 ±5
Time (post-dose)	-	-	-	-	-	-	-	-	-	-	-	-	-	72h	-	-
Electrocardiogram (ECG)	X	X						X							X	
Diffusing Capacity (DLCO)	X	X[5]			X			X			X				X	
Spirometry	X	X[5]			X			X			X				X	
High Resolution CT of Chest	X[17]														X	
Thyroid Hormones		X														
Autoimmune Serology[18]	X[19]															

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6-Minute Walk Test		X			X			X			X				X	
Autoantibody Profiling		X													X	

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Immunogenicity[8]		X			X			X			X				X	
PK blood collection[8]		X			X			X			X		X	X[9]	X	

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CCI

Epoch	Screening	Treatment[2]														
Visit Name	Screening	Treatment														
Visit Numbers[1]	1	101[13]	103	104	105	106	107	108	109	110	111	112	113	114	115	199
Weeks	-6 to -1	1	5	9	13	17	21	25	29	33	37	41	45	45	49	49
Days	-42 to -1	1	29 ±2	57 ±5	85 ±5	113 ±5	141 ±5	169 ±5	197 ±5	225 ±5	253 ±5	281 ±5	309 ±5	312 ±5	337 ±5	337 ±5
Time (post-dose)	-	-	-	-	-	-	-	-	-	-	-	-	-	72h	-	-
Study drug administration		X[11]	X	X	X	X	X	X	X	X	X	X	X			
Methylprednisolone		X[11]														

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Telephone follow-up																
Epoch completion information	X															X
Concomitant medications	As Required															
Adverse Events	As Required															
Serious Adverse Events	As Required															

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[1] Visit structure given for internal programming purpose only
[2] All assessments to be conducted before dosing
[3] As required (see Section 8.6 Safety for additional information)
[4] Body Height at screening only
[5] To be completed prior to dosing

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[8] One additional pharmacokinetic and immunogenicity sample should be collected in case of a hypersensitivity reaction or adverse event that could be related to immunogenicity
[9] PK sample to be collected 72 hours post previous dose.

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[11] 250 mg i.v. methylprednisolone (with or without additional antihistamine and/or paracetamol medication, at the discretion of the investigator) is mandatory prior to the first dose (V101). Additional information on this process can be found in the SOM.
[12] The purpose of this assessment is to report Adverse Events and changes in Concomitant Medication.
[13] The subject will remain in clinic for 6 hours post-dose for observation

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[17] If the HRCT was performed at the time of the initial screening, then it will not be repeated if the patient is re-screened.

[18] Results are not required to confirm eligibility.

[19]If the blood sample for autoantibodies was collected and analyzed by the Central Lab at the time of the initial screening, then repeat samples will not be collected if the patient is re-screened.

8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators a proposed ICF that complies with the International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) guideline and regulatory requirements and is considered appropriate for this study. The ICF will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed ICF suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject ICF and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification (IN) or an Aggregate Safety Finding. New information might require an update to the ICF and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

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A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

Refer to the SOM for a complete list of ICFs included in this study.

8.3 Subject screening

It is permissible to re-screen a subject if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

A new ICF will need to be signed if the investigator chooses to re-screen a subject after the subject has failed screening, and the subject will be assigned a new subject number.

Re-screened patients will complete all assessments listed for the Screening Visit in the Assessment Schedule (Section 8.1) with the following exceptions:

- If the HRCT was performed at the time of the initial screening, then it will not be repeated.
- If the blood sample for autoantibodies was collected and analyzed by the Central Lab at the time of the initial screening, then repeat samples will not be collected.

Information on what data should be collected for screening failures is outlined in the SOM.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the SOM.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.4.1 Alcohol Test, Drug Screen, and Cotinine Test

All subjects will be screened for substances of abuse and cotinine. See the SOM for details.

8.4.2 Hepatitis screen

All subjects will be screened for Hepatitis B and C. See the SOM for details.

8.4.3 HIV screen

All subjects will be screened for HIV. See the SOM for details.

8.4.4 Tuberculosis test

All subjects will be screened for Tuberculosis. See the SOM for additional details.

8.4.5 Autoimmune Serology

All subjects will be screened for the following auto-antibodies at screening: RF, ANA, anti-dsDNA, anti-CCP, Scl-70, SSA (anti-Ro), SSB (anti-La), anti-RNP, anti-Smith, Jo-1, PL-7, PL-12, EJ, OJ, SRP, Ku, Mi-2, anti-PM/Scl. Results are not required to confirm eligibility.

8.4.6 Thyroid Hormones

All subjects will be screened for the following thyroid function tests at Visit 101: free thyroxine, total thyroxine, triiodothyronine and thyroid-stimulating hormone.

8.5 Efficacy / Pharmacodynamics

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8.5.1 Spirometry

Spirometry testing will be performed according to the ATS guidelines (Miller et al 2005) at screening to assess patients' eligibility for the study and as detailed in the Assessment schedule (Section 8.1).

The spirometry equipment will be supplied to each site for the study. The same spirometry equipment should be used for all assessments performed by a subject. A limited number of staff, as designated by the investigator, will evaluate all patients at all visits throughout the entire trial. Where possible the same technician should perform all maneuvers for an individual subject. All staff conducting the spirometry tests must have received appropriate training which must be documented. Information on the procedures can be found in the SOM.

8.5.2 Diffusing Capacity (DLCO)

Diffusion capacity will be determined according to ATS guidelines (Graham et al 2017). Measurements will include DLCO and VA. Additional information is provided in the SOM.

8.5.3 High Resolution CT of Chest

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8.5.4 6-Minute Walk Test

A standardized six-minute walk test (6MWT) will be carried out by a trained technician in accordance with the guidelines (Holland et al 2014). See SOM for details.

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8.5.6 Clinical Outcome Assessments (COAs)

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8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed.

The safety assessments include:

- Adverse events, vital signs, physical exams, safety labs (hematology, chemistry, urinalysis), and electrocardiogram (ECG)
- Immunoglobulins

8.6.1 Physical Examination

See Site Operations Manual for details.

8.6.2 Body Weight

Body weight will be recorded during the study. Refer to the Assessment schedule (Section 8.1).

8.6.3 Vital Signs

Body temperature, blood pressure, oxygen saturation and pulse rate will be recorded at multiple time points during the study. Please refer to the Assessment schedule (Section 8.1) and the SOM for additional information.

8.6.4 Clinical Chemistry

The chemistry panel will include: albumin, alkaline phosphatase, total and direct bilirubin, calcium, chloride, creatinine, creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), α-amylase, γ-glutamyltransferase (GGT), glucose, sodium, potassium, inorganic phosphorus, total protein, lactate dehydrogenase (LDH), serum bicarbonate, magnesium, blood urea nitrogen (BUN), uric acid and lipase.

8.6.5 Hematology

The hematology panel will include: hemoglobin, hematocrit, red blood cell count, white blood cell count including differential cell counts (lymphocytes, monocytes, neutrophils, eosinophils, and basophils) and platelet count.

8.6.6 Urinalysis

A urine sample (approx. 30 mL) will be obtained midstream in order to avoid contamination with epithelial cells and sediments, and to allow proper assessments.

Semi-quantitative 'dipstick' evaluation of the urine for the following parameters will be performed centrally: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for albumin, nitrite, leucocytes and/ or blood, the sample will be sent for culture and for microscopic analysis of white blood cells, red blood cells and casts.

8.6.7 Immunoglobulin

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8.6.8 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the SOM.

ECG parameters will include: PR interval, QRS duration, heart rate, RR interval, QT interval, QTc. The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Clinically significant abnormalities must be reported in the AE CRF.

8.6.9 Pregnancy and assessments of fertility

Pregnancy Testing

All WOCBP will have pregnancy testing. See the Assessment schedule (Section 8.1), for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements*. A serum pregnancy test is required for the screening visit (Visit 1), but urine pregnancy testing is acceptable for all other visits. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

*Additional pregnancy testing might be performed if requested per local requirements.

Refer to Section 9.6 for details on Reporting Pregnancy.

Assessments of Fertility

Refer to Section 4.2 for criteria to determine women that are not of child bearing potential.

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject, regardless of reported reproductive/menopausal status at Screening.

8.7 Pharmacokinetics

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8.8 Other assessments

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8.8.3 Immunogenicity

Immunogenicity (IG) samples will be obtained and evaluated in all subjects including the placebo group.

In case of suspected allergic hypersensitivity, the subject should return to the site and a sample to assess immunogenicity will be collected.

In case of positive immunogenicity, backup of previous pre-dose PK samples could be used to better characterize the onset of immunogenicity response.

Follow instructions outlined in the SOM and central laboratory manual regarding sample collection, numbering, processing, and shipment.

Immunogenicity analytical method(s)

A bridging ELISA method that is designed to detect the presence of anti-VAY736 antibodies in human serum will be used. The method contains three components: (1) Screen assay, which identifies initial positive or negative samples, (2) Confirmation assay, which assesses specificity of the positive screen samples, and (3) Titration assay which estimates the level of antibody for the confirmed positive samples.

The detailed method for immunogenicity assessment will be described in the Bioanalytical Data Report.

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9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver and kidney related events are included in Appendix 1 and Appendix 2, respectively.

Adverse events should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The severity grade:
   mild: usually transient in nature and generally not interfering with normal activities
   moderate: sufficiently discomforting to interfere with normal activities
   severe: prevents normal activities
2. its relationship to the study treatment
   - Yes or
   - No
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.
   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - no action taken (e.g. further observation only)
   - investigational treatment dosage increased/reduced
   - investigational treatment interrupted/withdrawn
   - concomitant medication or non-drug therapy given
   - hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)
6. its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications (IN). Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

Refer to the SOM for data capture methodology regarding AE collection for subjects that fail screening.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g., evaluate candidacy for lung transplantation)
    - elective or pre-planned treatment for a pre-existing condition (that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to ICH-E2D Guidelines).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to ICH-E2D Guidelines).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2.

9.2.2 SAE reporting

Screen Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

Randomized Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until a minimum of 30 days after the last administration of study treatment must be reported to Novartis within 24 hours of learning of its occurrence as described below. The subject will be followed for up to two years after last administered dose.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow-up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the SOM regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate CRFs

Please refer to Table 15-1 - Appendix 1 for complete definitions of liver laboratory triggers and liver events.

Follow-up of liver events

Every liver event defined in Table 15-1 - Appendix 1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 15-2 - Appendix 1.

- Repeat liver chemistry tests (ALT, AST, Total Bilirubin (TBL), Prothrombin Time (PT)/International Normalized Ratio (INR), Alkaline Phosphatase (ALP) and Gamma-Glutamyl Transferase (G-GT)) to confirm elevation within 48-72 hours.

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported on the unscheduled local laboratory CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to Section 7.2 (Discontinuation of study treatment)), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include
    - Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and GGT. If total bilirubin is elevated > 2 x Upper Limit of Normal (ULN), fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Retesting should be continued up to resolution.
    - Obtaining a more detailed history of symptoms and prior or concurrent diseases.
    - Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
    - Exclusion of underlying liver disease, as specified in Table 15-3 - Appendix 1.
    - Imaging such as abdominal US, CT or MRI, as appropriate

- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the SOM for additional details.

9.4 Renal safety monitoring

Every renal laboratory trigger or renal event as defined in Table 16-1 - Appendix 2 must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the SOM for additional details.

9.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Chief Medical Office and Patient Safety (CMO&PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (AE) CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Chief Medical Office and Patient Safety (CMO& PS). As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Guidance for capturing study treatment errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be **reported to Novartis within 24 hours** of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO&PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (eCRFs) with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

Continuous remote monitoring of each site's data may be performed by Novartis and/or the Contract Research Organization (CRO) working on behalf of Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed

according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 U.S. Code of Federal Regulation (CFR) Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the SOM and Assessment schedule (Section 8.1) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

10.3 Database management and quality control

The CRO working on behalf of Novartis will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the CRO working on behalf of Novartis who will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

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10.4 Data Monitoring Committee

The study will be using a Data Monitoring Committee (DMC). A DMC is a group of professionals, experienced in clinical care and/or clinical research, assembled to provide additional safety oversight to a clinical study. The DMC will operate in accordance with a DMC charter which will be completed prior to FPFV. The DMC will meet on a regular basis to review trial safety data; and the DMC will meet on an *ad-hoc* basis to review individual SAEs. Additional information can be found about the DMC in Section 7.5.

10.5 Adjudication Committee

The study will be using an Adjudication Committee. The committee will be reviewing a subset of SAE(s), in a blinded fashion, in order to confirm the diagnosis of accute exacerbation of IPF and, if necessary, determine the cause of any deaths (these are efficacy endpoints). The Adjudication Committee will have a charter completed prior to FPFV.

11 Data analysis

The primary efficacy and safety analysis will occur when the last randomized patient completes the treatment epoch unless the study is stopped for futility or early efficacy at the interim analysis, in which case the interim analysis will be called the primary efficacy and safety analysis.

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Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement who received any study drug and with no protocol deviations that impact on PK data.

The IG analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) IG concentration measurement, who received any study drug and with no protocol deviations that impact on IG data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

11.4 Analysis of the primary variable(s)

The primary objective of the study is to assess the efficacy of VAY736 on top of current standard-of-care therapy (pirfenidone, nintedanib, or no IPF-specific treatment) using FVC (ml) at the end of treatment epoch (48 weeks of treatment) in patients with idiopathic pulmonary fibrosis.

11.4.1 Primary Variable(s)

The primary efficacy endpoint is the change from baseline in FVC (ml).

11.4.2 Statistical model, hypothesis, and method of analysis

The following hypothesis will be tested for VAY736+SoC versus placebo+SoC:

H_0: There is no difference or worsening in change from baseline in FVC (ml) from baseline to 48 weeks of treatment between VAY736+SoC and placebo+SoC

H_1: There is an improvement in change from baseline in FVC (ml) from baseline to 48 weeks of treatment between VAY736+SoC and placebo+SoC

Test will be conducted at a one-sided 10% level and 2-sided 80% CI of the estimates will be displayed.

The primary variable, change from baseline in FVC (ml), after 48 weeks of treatment will be analyzed using Mixed Effects Model for Repeated Measures (MMRM). The model will include treatment and visit as fixed effects, standard of care treatment (Nintedanib, Pirfenidone, neither) as factor and baseline value as a covariate, treatment-by-visit and baseline-by-visit as interaction terms. The patient effect will be assumed to be random and unstructured covariance matrix will be assumed for within-patient variation. The main comparison will be a contrast between treatment groups at 48 weeks of treatment. This approach assumes data is Missing At Random (MAR).

Summary statistics of change from baseline in FVC by epoch and treatment will be presented.

11.4.3 Handling of missing values/censoring/discontinuations

Given the severity of disease and the likelihood of some missing data, this study will also include approaches to assess treatment under the assumption of missing not at random.

11.4.4 Sensitivity analyses

A sensitivity analysis that uses alternative approaches to missing data will also be evaluated.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

Survival analysis

At the end of the treatment epoch, the Kaplan-Meier estimates of the proportion of patients with the event of interest, along with 80% two-sided confidence intervals using Greenwood's formula, will be provided. In addition, the Kaplan-Meier estimates will be plotted against time.

The two treatment groups will be compared using a one-sided logrank test at the 10% significance level. The hazard ratio and its associated 80% two-sided confidence intervals will be estimated.

Event of interest is defined as:

1. All-cause mortality
2. IPF-related mortality

Progression-free survival (PFS) analysis

Same survival analysis as defined above will be produced at the end of the treatment epoch for the following event of interest:

1. Events, defined as: death (all-cause mortality) **OR** "progression" (relative reduction in FVC $\geq$ 10%)
2. Events, defined as: death (IPF-related mortality) **OR** "progression" (relative reduction in FVC $\geq$ 10%)

Disease progression

At the end of the treatment epoch, the Kaplan-Meier estimates of the proportion of patients with progression, along with 80% two-sided confidence intervals using Greenwood's formula, will be provided. The two treatment groups will be compared using a one-sided logrank test at the 10% significance level. The hazard ratio and its associated 80% two-sided confidence intervals will be estimated.

1. Progression, defined as: relative reduction in FVC ≥ 10%
2. Progression, defined as: relative reduction in DLcO ≥ 15%
3. Progression, defined as: absolute reduction in 6MWD ≥ 50 m

Composite endpoint

At the end of the treatment epoch, the Kaplan-Meier estimates of the proportion of patients with event of interest, along with 80% two-sided confidence intervals using Greenwood's formula, will be provided, where events of interest is defined as below. The two treatment groups will be compared using a one-sided logrank test at the 10% significance level. The hazard ratio and its associated 80% two-sided confidence intervals will be estimated.

1. death (all-cause mortality), **OR** relative reduction in FVC≥10%, **OR** relative reduction in DLcO ≥15%, **OR** relative reduction in 6MWD ≥50m
2. death (IPF-related morality), **OR** relative reduction in FVC≥10%, **OR** relative reduction in DLcO ≥15%, **OR** relative reduction in 6MWD ≥50m

Pulmonary physiology

Change from baseline to the end of treatment epoch in DLCO will be analyzed by fitting the same model as described for the primary endpoint above in addition to summary statistics by treatment.

Exercise capacity

Change from baseline to the end of treatment epoch in 6-minute walk distance and in distance-saturation product will be analyzed by fitting the same model as described for the primary endpoint above in addition to summary statistics by treatment.

Gas exchange

Change from baseline to the end of treatment epoch in resting oxygen saturation (on room air) will be analyzed by fitting the same model as described for the primary endpoint above in addition to summary statistics by treatment.

11.5.2 Safety

Vital signs

All vital signs data will be listed by treatment group, subject, and epoch/visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by epoch, treatment and visit/time.

ECG evaluations

All ECG data will be listed by treatment group, subject and epoch/visit/time, abnormalities will be flagged. Summary statistics will be provided by epoch, treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and epoch/visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by epoch, treatment and visit/time.

Adverse events

All information obtained on adverse events will be displayed by treatment group, epoch and subject.

The number and percentage of subjects with treatment-emergent adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple treatment-emergent adverse events within a body system is only counted once towards the total of this body system.

A treatment-emergent adverse event is defined as any adverse event that develops on or after the time of the first drug intake or any event already present that worsens following exposure to the study treatment.

All adverse events will be listed.

11.5.3 Pharmacokinetics

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Commercially Confidential Information

11.5.4 Pharmacokinetic / pharmacodynamic interactions

Commercially Confidential Information

11.5.5 Other assessments

Immunogenicity

Commercially Confidential Information

11.6 Analysis of exploratory variables

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

11.7 Sample size calculation

In total 58 subjects are going to be randomized to the study in a 1:1 randomization. Assuming a treatment period of 48 weeks with 2 arms, VAY736+Standard-of-Care (SoC) vs. Placebo+SoC, and standard deviation of 250 ml for FVC (ml); a total sample size of 58 patients with 48 weeks data will give at least 80% power to detect a treatment improvement in change from baseline in FVC (ml) between VAY736+SoC and Placebo+SoC of 160ml in patients with Idiopathic Pulmonary Fibrosis (IPF).

The sample size calculation is based on the primary efficacy endpoint of change from baseline in FVC (ml) at week 48. The criteria for this calculation aimed for a 90% level of proof that difference in change in FVC from baseline to week 48 between VAY736+SoC and placebo+SoC > 0 and the mean treatment+SoC effect is at least 110 ml better than placebo+SoC effect. The former targets proof that the treatment+SoC produces a statistically significant improvement in change from baseline in FVC, while the latter targets proof of clinical relevance.

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The overall type I error at the end of study will be approximately 12% under this sample size.

If more than 20% of the randomized patients have not completed the 48 weeks of treatment, per protocol, then patients may be replaced.

R software version 3.0.3 (Fisch et 2015) was used.

11.8 Power for analysis of key secondary variables

Not applicable

11.9 Interim analyses

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12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis by the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

12.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

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15 Appendix 1: Liver Event and Laboratory Trigger Definitions and Follow-up Requirements

Table 15-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	• 3 x ULN < ALT / AST ≤ 5 x ULN • 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • TBL > 2 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN: upper limit of normal

Table 15-2 Follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
	• Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	• Repeat LFT within 48 hours • If elevation persists, establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	• Discontinue the study treatment immediately • Hospitalize the subject	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c]

Criteria	Actions required	Follow-up monitoring
	• Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	(frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g., conmeds, med hx, lab) in the appropriate CRF	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion, investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, (Hepatitis B virus) HBV DNA; anti-Hepatitis C Virus (HCV), HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, GGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal Alert Criteria and Actions

Table 16-1 Specific Renal Alert Criteria and Actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50 % [+] **OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m²**	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Assess & document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+] Corresponds to KDIGO criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology. *(Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)*

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output

- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-2 Renal Event Follow-up

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in CRF • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
Monitor patient regularly (frequency at investigator's discretion) until - • Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event

17 Appendix 3: ATS/ERS/JRS/ALAT Diagnostic Guidelines

Figure 17-1 Diagnostic algorithm for IPF (Figure 3 in Raghu et al 2011)

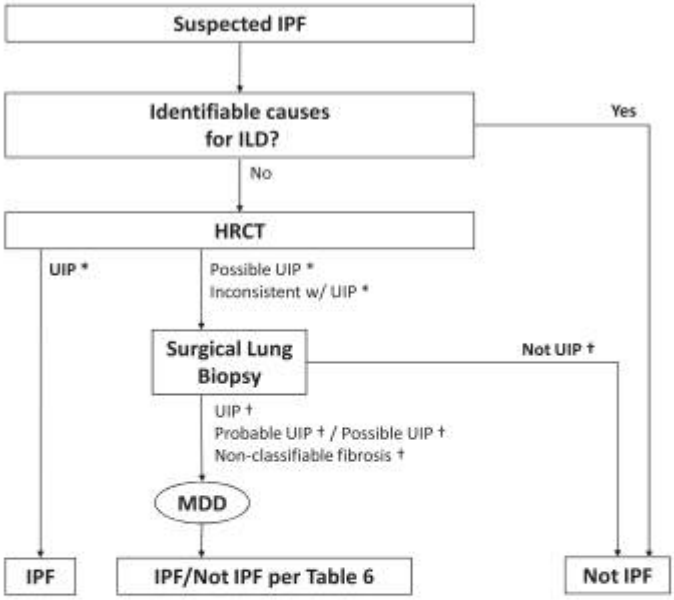

Figure 3. Diagnostic algorithm for idiopathic pulmonary fibrosis (IPF). Patients with suspected IPF (i.e., patients with unexplained dyspnea on exertion and/or cough with evidence of interstitial lung disease [ILD]) should be carefully evaluated for identifiable causes of ILD. In the absence of an identifiable cause for ILD, an HRCT demonstrating UIP pattern is diagnostic of IPF. In the absence of UIP pattern on HRCT, IPF can be diagnosed by the combination of specific HRCT and histopathological patterns. The accuracy of the diagnosis of IPF increases with multidisciplinary discussion (MDD) among ILD experts. *Refer to Table 4 for definitions. †Refer to Table 5 for definitions.

Table 17-1 High-resolution computed tomography criteria for UIP pattern (Table 4 in Raghu et al 2011)

TABLE 4. HIGH-RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (Any of the Seven Features)
• Subpleural, basal predominance • Reticular abnormality • Honeycombing with or without traction bronchiectasis • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Subpleural, basal predominance • Reticular abnormality • Absence of features listed as inconsistent with UIP pattern (*see* third column)	• Upper or mid-lung predominance • Peribronchovascular predominance • Extensive ground glass abnormality (extent > reticular abnormality) • Profuse micronodules (bilateral, predominantly upper lobes) • Discrete cysts (multiple, bilateral, away from areas of honeycombing) • Diffuse mosaic attenuation/air-trapping (bilateral, in three or more lobes) • Consolidation in bronchopulmonary segment(s)/lobe(s)

Definition of abbreviation: UIP = usual interstitial pneumonia.

Table 17-2 Histopathological Criteria for UIP pattern (Table 5 in Raghu et al 2011)

TABLE 5. HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

UIP Pattern (All Four Criteria)	Probable UIP Pattern	Possible UIP Pattern (All Three Criteria)	Not UIP Pattern (Any of the Six Criteria)
• Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution • Presence of patchy involvement of lung parenchyma by fibrosis • Presence of fibroblast foci • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column)	• Evidence of marked fibrosis / architectural distortion, ± honeycombing • Absence of either patchy involvement or fibroblastic foci, but not both • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column) OR • Honeycomb changes only‡	• Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation • Absence of other criteria for UIP (*see* UIP Pattern column) • Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (*see* fourth column)	• Hyaline membranes* • Organizing pneumonia*† • Granulomas† • Marked interstitial inflammatory cell infiltrate away from honeycombing • Predominant airway centered changes • Other features suggestive of an alternate diagnosis

Definition of abbreviations: HRCT = high-resolution computed tomography; UIP = usual interstitial pneumonia.

* Can be associated with acute exacerbation of idiopathic pulmonary fibrosis.

† An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.

‡ This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.

Table 17-3 Combination of HRCT and surgical lung biopsy for the diagnosis of IPF (Table 6 in Raghu et al 2011)

HRCT Pattern*	Surgical Lung Biopsy Pattern* (When Performed)	Diagnosis of IPF?†
UIP	**UIP** **Probable UIP** **Possible UIP** **Nonclassifiable fibrosis‡**	**YES**
	Not UIP	No
Possible UIP	**UIP** **Probable UIP**	**YES**
	Possible UIP Nonclassifiable fibrosis	Probable§
	Not UIP	No
Inconsistent with UIP	UIP	Possible§
	Probable UIP Possible UIP Nonclassifiable fibrosis Not UIP	No

Definition of abbreviations: HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

Bold type indicates combinations of HRCT and surgical lung biopsy patterns that correspond with a diagnosis of IPF (a YES in the far right column). The combination of UIP HRCT and probable UIP or possible UIP or Nonclassifiable fibrosis (surgical lung biopsy patterns) (for example) equals a diagnosis of IPF; the combination of UIP HRCT and Not UIP (surgical lung biopsy pattern) does not make the diagnosis of IPF.

* Patterns as described in Tables 4 and 5.

‡ Nonclassifiable fibrosis: Some biopsies may reveal a pattern of fibrosis that does not meet the above criteria for UIP pattern and the other idiopathic interstitial pneumonias (1) (*see text*). These biopsies may be termed "nonclassifiable fibrosis."

† The accuracy of the diagnosis of IPF increases with multidisciplinary discussion (MDD). This is particularly relevant in cases in which the radiologic and histopathologic patterns are discordant (e.g., HRCT is inconsistent with UIP and histopathology is UIP). There are data to suggest that the accuracy of diagnosis is improved with MDD among interstitial lung disease experts compared to clinician-specialists in the community setting (126); timely referral to interstitial lung disease experts is encouraged.

§ Multidisciplinary discussion should include discussions of the potential for sampling error and a re-evaluation of adequacy of technique of HRCT. NOTE: In cases with an "inconsistent with UIP" HRCT pattern and a "UIP" surgical lung biopsy pattern, the possibility of a diagnosis of IPF still exists and clarification by MDD among interstitial lung disease experts is indicated.

Raghu et al 2011