

Official Title: An Exploratory Multicenter, Open-Label, Single Arm Study of the Safety and Tolerability of Pirfenidone (Esbriet®) in Combination With Nintedanib (Ofev®) in Patients With Idiopathic Pulmonary Fibrosis

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PROTOCOL

TITLE: AN EXPLORATORY MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY OF THE SAFETY AND TOLERABILITY OF PIRFENIDONE (ESBRIET®) IN COMBINATION WITH NINTEDANIB (OFEV®) IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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TEST PRODUCT: Pirfenidone (Esbriet®) and nintedanib (Ofev®)

MEDICAL MONITOR: [REDACTED], MD

SPONSOR: F. Hoffmann-La Roche Ltd

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Version 3: 21 June 2016

FINAL PROTOCOL APPROVAL

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE: AN EXPLORATORY MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY OF THE SAFETY AND TOLERABILITY OF PIRFENIDONE (ESBRIET[®]) IN COMBINATION WITH NINTEDANIB (OFEV[®]) IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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TEST PRODUCT: Pirfenidone (Esbriet[®]) and nintedanib (Ofev[®])

MEDICAL MONITOR: [REDACTED], MD

SPONSOR: F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please retain the signed original of this form for your study files. Please return a copy to the Sponsor or their designee. Contact details will be provided to the investigator prior to the study start.

PROTOCOL SYNOPSIS

TITLE: AN EXPLORATORY MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY OF THE SAFETY AND TOLERABILITY OF PIRFENIDONE (ESBRIET[®]) IN COMBINATION WITH NINTEDANIB (OFEV[®]) IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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TEST PRODUCT: Pirfenidone (Esbriet[®]) and nintedanib (Ofev[®])

PHASE: IV

INDICATION: Idiopathic Pulmonary Fibrosis

SPONSOR: F. Hoffmann-La Roche Ltd

OBJECTIVES AND ENDPOINTS

The primary objective for this study is to investigate the safety and tolerability of adding nintedanib to treatment with pirfenidone in patients with Idiopathic Pulmonary Fibrosis (IPF).

Eligible patients must be receiving chronic treatment with pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days. In patients eligible for this study, nintedanib will be added as an additional treatment for IPF (combination treatment) for 24 weeks.

STUDY OBJECTIVES

Primary Safety Objective

- Proportion of patients who complete 24 weeks of combination treatment on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d

Secondary Safety Objectives

Secondary Safety Objectives are:

- Proportion of patients who discontinue pirfenidone, nintedanib, or both study treatments because of adverse events before the Week 24 Visit
- Total number of patient days of combination treatment with pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d
- Total number of days from the initiation of combination treatment to discontinuation of pirfenidone, nintedanib, or both study treatments
- Frequency and timing of adverse events (AE) and Serious Adverse Events (SAEs)

Exploratory Efficacy Objectives

[REDACTED]

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[REDACTED]

Patient-Reported Outcome Objective

The following patient-reported outcomes (PRO) for this study will be analyzed in an exploratory manner:

[REDACTED]

Biomarker Study

- Blood samples will be collected for the purposes of assessing the pharmacodynamics effect of nintedanib on pirfenidone or IPF-related biomarkers.

STUDY DESIGN

DESCRIPTION OF THE STUDY

This is a multicenter, international, open-label, single-arm safety and tolerability study of pirfenidone/nintedanib combination treatment in patients with IPF who have been on a stable dose of pirfenidone with demonstrated tolerability. In this study, a stable pirfenidone dose will be defined as 1602–2403 mg/d (801 mg twice daily [BID] or three times daily [TID]). Up to approximately 60 clinical centers in the US, Europe, and Canada are expected to enroll up to approximately 80 patients. Patients who are withdrawn from the study will not be replaced. The study design is presented in the [figure below](#).

At the start of Screening, patients will have been on pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days; also, the dose must be expected to remain within that range throughout the study. In addition, in the 28 days before the start of Screening, patients must not have experienced either a new or ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an interruption of pirfenidone treatment for > 7 days for any reason.

After providing informed consent and discussing the risks and benefits of the study with the Investigator, patients will be required to [aper](#) and/or discontinue all prohibited medications ([Section 4.4.2](#)) at least 28 days before the start of Screening; this is the Washout Period. Patients will be instructed to continue their commercial pirfenidone during the Washout Period. If a prohibited medication must be tapered, tapering must start early enough that the patient has discontinued the medication 28 days before the start of Screening. After completing Washout, patients will enter Screening, which lasts up to 21 days; during Screening, patients will be evaluated for eligibility based on the inclusion and exclusion criteria. Patients not taking a prohibited medication will forgo Washout and directly enter Screening. At screening, after eligibility criteria have been met, patients may be provided pirfenidone for the study and will be instructed on proper use. In this case, patients will be instructed to stop taking their commercial pirfenidone and start taking the study provided pirfenidone.

During Screening, patients on a stable dose of pirfenidone may return for the Baseline Visit (Study Day 1) as soon eligibility has been confirmed. At this visit, they will have nintedanib added to the ongoing pirfenidone treatment. Nintedanib dosing will start at 100 mg once daily (QD) and

be titrated to 150 mg BID over 15 days, as tolerated, according to the schedule provided in protocol Table 1.

The Sponsor will supply pirfenidone and nintedanib for use in the study; nintedanib will be supplied in 100 mg and 150 mg capsules to facilitate temporary dose reduction if required for the management of AEs.

Combination treatment will continue through Week 24, with monitoring by office visits and telephone contacts. Blood samples will be obtained from all patients for analysis of clinical laboratory values.

Patients will be encouraged to remain on stable doses of pirfenidone (1602–2403 mg/d) and nintedanib (200–300 mg/d) throughout the combination-treatment period, unless dosing is modified to manage an AE. Patients will return to the clinic for a final Follow-up Visit 28–35 days after the completion of combination treatment.

If one or both study treatments are prematurely discontinued or interrupted for ≥ 28 consecutive days, nintedanib treatment will end as will the patient's participation in the study; whether commercial pirfenidone treatment continues will be left to the judgment of the Investigator. The patient will then return to the clinic as soon as possible (≤ 7 days after the decision to discontinue nintedanib) for an Early Discontinuation Visit.

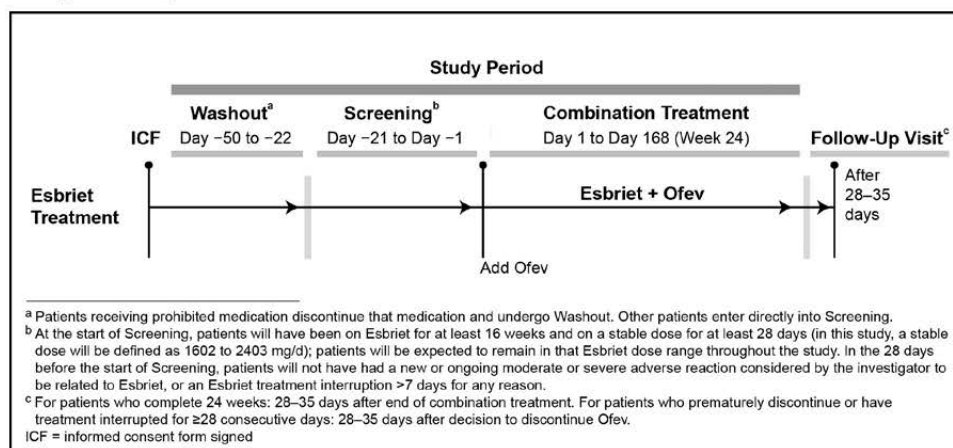
In addition, 28–35 days after the decision to discontinue nintedanib, the patient will return for a final Follow-up Visit.

A patient diary will be used to record AEs, daily dosing adherence for both pirfenidone and nintedanib, and concomitant medication use from the screening visit to the final Follow-up Visit. Also, patients will receive a wallet card that provides important information relevant to study participation.

On completion of study participation, patients may be prescribed appropriate IPF treatment at the discretion of the treating physician.

An independent Data Monitoring Committee (iDMC) will review safety data and advise on study conduct at least two three times during the study: when the first approximately 20 patients have completed 8 weeks of combination treatment or permanently discontinued study treatments, when approximately 50% of the total patient group has completed 12 weeks of combination treatment or permanently discontinued study treatments and when approximately 75% of the total patient group has completed 24 weeks of combination treatment or permanently discontinued study treatments. Additional ad hoc meetings or data reviews can be requested at any time by the iDMC or the Sponsor, if warranted.

Design of Study



NUMBER OF PATIENTS

Number of patients to be enrolled: approximately 80

TARGET POPULATION

Inclusion Criteria

Eligible patients for this study must meet the following criteria for study entry:

20. Written informed consent to participate in the study
21. Male or female, and age 40 through 80 years old at the start of Screening (inclusive).
22. At the start of Screening, on pirfenidone for at least 16 weeks and on a stable dose for at least 28 days (in this study, a stable dose will be defined as 1602–2403 mg/d); the dose must be expected to remain in that range throughout the study.
23. Documented diagnosis of IPF, per the Investigator per using the criteria of the 2011 American Thoracic Society / European Respiratory Society / Japanese Respiratory Society / Latin American Thoracic Association guidelines
24. The value from pulmonary function test results (from documented pulmonary function laboratory reports) measured at the screening visit as follows:
 - Percent predicted FVC \geq 50%.
 - Percent predicted DLco (or carbon monoxide transfer capacity converted to DLco) \geq 30%
25. Able to understand the importance of adherence to the study treatment regimen and the study protocol, and willing to follow all study requirements, including the concomitant medication restrictions, throughout the study.
26. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of $< 1\%$ per year, during the treatment period and for at least 3 months after the final Follow-up Visit.
 - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
 - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
 - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
 - Barrier methods must always be supplemented with the use of a spermicide.
27. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
 - With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least for at least 4 months after the final Follow-up Visit. Men must refrain from donating sperm during this same period.
 - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least for at least 4 months after the final Follow-up Visit.
 - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g.,

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calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Clinical evidence of any active infection which according to the judgment of the investigator may interfere with study conduct, measurement of pulmonary function, or impact the course of IPF.
2. In the 28 days before the start of Screening, any new or ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an pirfenidone treatment interruption > 7 days for any reason.
3. Any condition that is likely to result in death in the 12 months after the start of Screening.
4. Lung transplantation anticipated in the 12 months after the start of Screening.
5. Any planned significant surgical intervention from the start of Screening through the final Follow-up Visit. This does not include minor surgical procedures (e.g., excision of a localized basal cell carcinoma).
6. Known hypersensitivity to the active substance or any excipient of either pirfenidone or nintedanib.
7. Any condition that, in the Investigator's judgment, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone or nintedanib.
8. Mild (Child Pugh A), moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment.
9. Severe renal impairment (creatinine clearance < 30 mL/min by the Cockcroft-Gault calculation), including end-stage renal disease requiring dialysis.
10. History or risk of gastrointestinal (GI) tract perforation.
11. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) in the 6 months before the start of Screening, including but not limited to, the following:
 - Unstable angina pectoris or myocardial infarction.
 - Congestive heart failure expected to require hospitalization during the study.
 - Uncontrolled clinically significant arrhythmias.
12. Electrocardiogram (ECG) with a heart-rate-corrected QT interval (corrected using Fridericia's formula, QTcF) \geq 500 ms at Screening, or a family or personal history of long QT syndrome.
13. Bleeding risk: genetic predisposition to bleeding, a hemorrhagic event in the 12 months before the start of Screening, or abnormal laboratory coagulation parameters. Patients who require fibrinolysis, full-dose therapeutic anticoagulation (e.g., vitamin K antagonists, dabigatran, heparin, hirudin), high-dose antiplatelet therapy, or other therapy that may substantially increase bleeding risk are excluded.

Note: the following are permitted: prophylactic low-dose heparin or heparin flush as needed for maintaining an indwelling intravenous device (e.g., enoxaparin 4000 IU SC per day), as well as prophylactic use of antiplatelet therapy (e.g., acetylsalicylic acid up to 325 mg/d, clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy).
14. Use of strong CYP1A2 inhibitors (e.g., fluvoxamine, enoxacin) in the 28 days before the start of Screening.
15. Use of inhibitors of P-glycoprotein (e.g., ketoconazole, erythromycin) or CYP3A4 (e.g., ketoconazole, erythromycin) or their inducers (e.g., rifampicin, carbamazepine, phenytoin, St John's wort) in the 28 days before the start of Screening.
16. History of alcohol or substance abuse in the 2 years before the start of Screening.

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17. Use of any tobacco product in the 12 weeks before the start of Screening, or an unwillingness to abstain from their use through the final Follow-up Visit.
18. In the judgment of the Investigator, not a suitable candidate for enrollment, or unlikely or unable to comply with the requirements of this study.
19. Use of any investigational therapy in a clinical study protocol in the 28 days before the start of Screening
20. Pregnancy or lactation.
21. Hypersensitivity to peanuts.
22. Hypersensitivity to soy.

END OF STUDY AND LENGTH OF STUDY

Length of Study

The expected study length is up to 21 months

End of Study

January 2018

INVESTIGATIONAL MEDICINAL PRODUCTS

PIRFENIDONE

Pirfenidone is approved in a 267 mg capsule dosage form.

The recommended dose is 801 mg (i.e., three 267 mg capsules) TID, at the same times each day, taken with food (total dose, 2403 mg/d). At the beginning of the study, patients will be on a stable pirfenidone dose, as defined in the inclusion criteria.

NINTEDANIB

Nintedanib is approved in 100 mg and 150 mg capsule dosage forms.

The recommended dose is 150 mg BID, approximately 12 hours apart, at the same times each day, taken with food (total dose, 300 mg/d). Both 100 mg and 150 mg capsules will be supplied to facilitate temporary dose reduction if required to manage AEs.

STATISTICAL METHODS

PRIMARY ANALYSIS

The analysis population will be the Safety Population. It will consist of all patients who received at least one dose of nintedanib or pirfenidone at the Baseline Visit (Day 1).

AEs will be coded to a preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE). Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

Because this is a safety and tolerability study that is not designed to assess efficacy, no formal statistical hypotheses for efficacy will be assessed. The efficacy analyses will be limited to descriptive statistics.

Data summaries will be provided for baseline characteristics; patient disposition; extent of exposure; the number and proportion of patients who complete 24 weeks on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d (with 95% confidence interval [CI]); the numbers and proportions of patients with a dose reduction or a dose interruption; the number and proportion of patients who discontinued combination treatment because of a AE (with 95% CI); the total number of days on combination treatment at an pirfenidone dose of 1602–

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2403 mg/d and a nintedanib dose of 200–300 mg/d; the total number of days from the start of combination treatment to discontinuation of one or both study treatments; the final prescribed doses of pirfenidone and nintedanib; and the reasons for premature discontinuation of combination treatment.

AEs and SAEs leading to discontinuation will be summarized by incidence, severity, seriousness, and relationship to treatment. Additional summaries will be provided for the numbers and proportions of patients with a Major Adverse Cardiac Event (MACE), a cerebrovascular event, a bleeding event, or a thromboembolic event; the numbers and proportions of patients discontinuing combination treatment for a liver test abnormality, a GI event, or a photosensitivity reaction/rash; the numbers and proportions of patients with an emergency department visit or hospitalization; and deaths.

Observed and change values for clinical laboratory and vital signs data will be summarized. Grade 3 and 4 laboratory abnormalities will be summarized by CTCAE grade, and shift tables by CTCAE grade will be provided.

ECG data will be summarized, presenting the numbers and proportions of patients with a maximum QTcF interval < 500 ms, 500–550 ms, and > 550 ms; with a maximum change from the baseline QTcF interval of ≤ 30 ms, 31–60 ms, and > 60 ms; and with ECG changes considered by the Investigator to be clinically significant.

DETERMINATION OF SAMPLE SIZE

A sample size of approximately 80 patients was selected based on the AE discontinuation rates after one year observed in the randomized Phase 3 pirfenidone studies and the randomized Phase 2 and 3 nintedanib studies (pirfenidone 14.6%, nintedanib 21%; per the 2014 US labels). Given that for pirfenidone the discontinuation rate after 24 weeks was 6%–8% in studies PIPF-004 and PIPF-006 it is a reasonable assumption that the nintedanib discontinuation rate was around 10% – 11%. As in this study of combination treatment, it is possible that the addition of nintedanib to ongoing pirfenidone treatment could increase the proportion of patients who discontinue because of an AE, given the overlap in the GI and hepatic effects of the two medications.

Assuming 85% of the patients complete 24 weeks of combination treatment, a sample size of 80 patients would be expected to yield an actual completion rate of 77.2% – 92.8% using a 95% CI.

Number of Patients who completed 24 weeks	Proportion of Patients who completed 24 weeks	Lower Bound of 95% CI	Upper Bound of 95% CI
76	95.0%	90.2%	99.8%
72	90.0%	84.4%	96.6%
68	85.0%	77.2%	92.8%
64	80.0%	71.2%	88.8%
60	75.0%	65.5%	84.5%

CI = confidence interval

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
%FVC	Percent predicted forced vital capacity
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATAQ	Asthma Therapy Assessment Questionnaire
ATS	American Thoracic Society
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CRO	Contract research organization
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
d	Day
DLco	Carbon monoxide diffusing capacity
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ERS	European Respiratory Society
FGF	Fibroblast growth factor
FDA	Food and Drug Administration
FEV1	Forced expiratory volume at one second
GCP	Good clinical practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HR	Heart rate
ICF	Informed consent form
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
JRS	Japanese Respiratory Society

Abbreviation	Definition
LATA	Latin American Thoracic Association
LPLV	Last patient, last visit
MACE	Major Adverse Cardiac Event
MedDRA	Medical Dictionary for Regulatory Activities
ms	Millisecond
NCI	National Cancer Institute
nRTK	Non-receptor tyrosine kinases
PDGF	Platelet-derived growth factor
PI	Package Insert
PI	Principal Investigator
PRO	Patient-reported outcome
QD	Once daily
QTcF	QT interval corrected using Fridericia's formula
RR	Respiratory rate
RTK	Receptor tyrosine kinases
SAE	Serious adverse event
SmPC	Summary of Product Characteristics
SOBQ	Shortness of breath questionnaire
SPF	Sun protection factor
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TGF- β	Transforming growth factor-beta
TID	Three times daily
TNF	Tumor necrosis factor
UIP	Usual interstitial pneumonia
UV-A	Ultraviolet A
UV-B	Ultraviolet B
ULN	Upper limit of normal
USP	U.S. Pharmacopeial Convention
USPI	US product information.
VEGF	Vascular endothelial growth factor
WHO	World Health Organization

1. BACKGROUND

1.1 BACKGROUND ON IDIOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is a devastating orphan disease of unknown etiology characterized by progressively decreasing lung volume, worsening dyspnea, and diminishing exercise capacity is recognized by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and Latin American Thoracic Association (LATA) as a distinct form of chronic fibrosing interstitial pneumonia. IPF occurs primarily in older adults, is limited to the lungs, and is defined by a radiologic and histopathologic pattern of usual interstitial pneumonia (UIP); it is the most common of the UIPs (Raghu et al. 2011).

IPF typically begins insidiously, with exertional dyspnea and nonproductive cough; the clinical course is unpredictable and ranges from slow and progressive respiratory decline to abrupt and accelerated deterioration. IPF is irreversible and ultimately fatal, with progressive disability and morbidity due to respiratory insufficiency. The diagnosis of IPF carries a bleak prognosis, with an estimated median survival after diagnosis of only 2.5 to 5 years (Bjoraker et al. 1998; Mapel et al. 1998; Douglas et al. 2000; Nicholson et al. 2000; King et al. 2001; Collard et al. 2003; Rudd et al. 2007; Fernández Pérez et al. 2010; Nathan et al. 2011; Kim et al. 2012).

Although the pathogenesis of IPF remains incompletely understood, the current view is that a series of microinjuries to the alveolar epithelium results in release of profibrotic mediators, causing fibroblast and myofibroblast proliferation, organization into fibroblastic foci, and excessive collagen deposition and accumulation (du Bois 2010).

1.2 BACKGROUND ON PIRFENIDONE AND NINTEDANIB

Pirfenidone

Pirfenidone is an antifibrotic agent with anti-inflammatory properties. It has been approved in a 267 mg capsule dosage form for the treatment of IPF in the United States (US), and for the treatment of mild to moderate IPF in the European Economic Area (EEA) and Canada. The recommended daily maintenance dose in patients with IPF is 2403 mg/d, administered as three 267 mg capsules (801 mg) three times daily (TID) with food, at the same times each day (Esbriet® EU SmPc and USPI 2014).

Pirfenidone is an orally active, small molecule (molecular weight, 185.2 g/mol) that exerts both antifibrotic and anti-inflammatory properties in a variety of animal models and *in vitro* systems. The broad antifibrotic activity of pirfenidone across organ systems has been demonstrated in more than 40 animal studies in models of fibrosis, including fibrosis of the liver, heart and kidney, as well as several models of lung fibrosis (Schaefer et al. 2011). In bleomycin-induced pulmonary fibrosis models, pirfenidone reduced visible lung pathology, lung tissue hydroxyproline content, edema (wet-to-dry lung weight), and the histologic score (Oku et al. 2008; PCLN-PIRF-009). Additionally, pirfenidone administration significantly suppressed bleomycin-induced increases in interleukin (IL)-1 β , IL-6, monocyte chemoattractant protein-1 and IL-12p40 in these models.

In cell-based systems, pirfenidone suppressed the proliferation of fibroblasts; attenuated the production of profibrotic cytokines, including platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF- β) from human macrophage cell lines; promoted release of collagenase from fibroblasts; and reduced the accumulation of extracellular matrix components, particularly collagen (Hirano et al. 2006; PCLN-PIRF-010).

Taken together, preclinical studies conducted *in vitro*, as well as data derived from animal models of fibrosis, provide evidence that pirfenidone reduces levels of profibrotic growth factors and cytokines, lessens collagen deposition, and reduces interstitial fibrosis—all of which are physiological elements thought to be dysregulated in IPF.

Nintedanib

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs) (Ofev[®] USPI 2014). It has been approved in the US in 100 and 150 mg capsule dosage forms for the treatment of IPF. The recommended daily maintenance dose in patients with IPF is 300 mg/d, administered as one 150 mg capsule two times daily (BID), approximately 12 hours apart, with food.

Nintedanib targets vascular endothelial growth factor (VEGF) receptors-1–3, PDGF receptors- α/β , and fibroblast growth factor (FGF) receptors-1–3 (Reck 2014). VEGF, PDGF, and FGF are mitogenic factors contributing to extracellular matrix proliferation and fibrogenesis (Kerbel 2008).

Although limited preclinical data exist regarding the antifibrotic potential of nintedanib, an antifibrotic pathway can be predicted based on its inhibition of PDGF, FGF, and VEGF (Antoniades et al. 1990; Battegay et al. 1990; Battegay et al. 1995; Kolb et al. 2001; Bonner 2004). Two dimers of PDGF, A and B, interact with PDGF- α or - β tyrosine kinase receptors, resulting in activation of downstream phosphatidylinositol-4,5-bisphosphate 3-kinase (Pi3K) and mitogen-activated protein kinase pathways. PDGF-A and PDGF-B strongly induce fibroblast mitosis and are potent chemottractants. *In vitro*, PDGF mediates TGF- β , IL-1, tumor necrosis factor (TNF)- α , FGF, and thrombin fibrotic responses. Macrophages in the bronchoalveolar lavage fluid of IPF patients produce four times the amount of PDGF compared with macrophages from normal lungs (Martinet et al. 1987).

Note: Investigators are recommended to refer to the Summary of Product Characteristics (SmPCs) / US-Package Insert (PI) of Esbriet[®] and Ofev[®] (2014) for additional details on results of non-clinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

The mechanism of action of pirfenidone in IPF has not been established (Esbriet[®] EU SmPc and USPI 2014), while nintedanib is thought to act by inhibiting multiple RTKs and nRTKs (Ofev[®] USPI 2014). Because multiple co-activated pathways are involved in the pathogenesis of IPF, experts have suggested that targeted therapies may work better in combination (Wuyts et al. 2014). Furthermore, experience in other pulmonary diseases (e.g., asthma, chronic obstructive pulmonary disease, and

pulmonary hypertension) has demonstrated the value of moving from monotherapy to combination therapy.

The positive benefit risk assessment of both drugs have been established in respective Phase II and Phase III programs which led to approval in the EU, the US, Japan and many other countries worldwide. Both drugs demonstrated that pulmonary function could be significantly improved in IPF patients, while the safety and tolerability profile was considered acceptable.

Considering the overlap in the gastrointestinal (GI) and hepatic AEs associated with these two drugs, it is worthwhile to characterize the safety and tolerability of nintedanib when added to pirfenidone as a combination treatment using the doses recommended in the respective pirfenidone and nintedanib labels.

This prospective study will evaluate the safety and tolerability of 24 weeks of nintedanib combination treatment in patients with IPF who are on a stable dose of pirfenidone with demonstrated tolerability. The study is not designed to evaluate the efficacy of combination treatment, nor is it designed to assess the safety and tolerability of adding pirfenidone to ongoing nintedanib treatment.

2. OBJECTIVES AND ENDPOINTS

The primary objective for this study is to investigate the safety and tolerability of adding nintedanib to treatment with pirfenidone in patients with IPF.

Eligible patients must be receiving chronic treatment with pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days. In patients eligible for this study, nintedanib will be added as an additional treatment for IPF (combination treatment) for 24 weeks.

2.1 SAFETY OBJECTIVES

This study is designed to assess the safety and tolerability of a combination treatment with pirfenidone and nintedanib. Consequently, the primary objectives of this study focus on safety and tolerability and not efficacy.

2.1.1 Primary Safety Objective

- Proportion of patients who complete 24 weeks of combination treatment on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d

2.1.2 Secondary Safety Objective

- Proportion of patients who discontinue pirfenidone, nintedanib, or both study treatments because of adverse events before the Week 24 Visit
- Total number of patient days of combination treatment with pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d
- Total number of days from the initiation of combination treatment to discontinuation of pirfenidone, nintedanib, or both study treatments
- Frequency and timing of Adverse (AE) and Serious Adverse Events (SAEs)

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2.2 EXPLORATORY EFFICACY OBJECTIVES

[REDACTED]

[REDACTED]

[REDACTED]

2.3 PATIENT-REPORTED OUTCOME OBJECTIVES

The following patient-reported outcomes (PRO) for this study will be analyzed in an exploratory manner:

[REDACTED]

2.4 BIOMARKER STUDY

Blood samples will be collected for the purposes of assessing the pharmacodynamics effect of nintedanib on pirfenidone or IPF-related biomarkers.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a multicenter, international, open-label, single-arm safety and tolerability study of pirfenidone/nintedanib combination treatment in patients with IPF who have been on a stable dose of pirfenidone with demonstrated tolerability. In this study, a stable pirfenidone dose will be defined as 1602–2403 mg/d (801 mg BID or TID). Up to approximately 60 clinical centers in the US, Europe, and Canada are expected to enroll up to approximately 80 patients. Patients who are withdrawn from the study will not be replaced. The study design is presented in [Figure 1](#).

At the start of Screening, patients will have been on pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days; also, the dose must be expected to remain within that range throughout the study, any dose reduction and/or interruption, please refer to [Section 4.3.2.6](#). In addition, in the 28 days before the start of Screening, patients must not have experienced either a new or ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an interruption of pirfenidone treatment for > 7 days for any reason. After providing informed consent and discussing the risks and benefits of the study with the Investigator, patients will be required to discontinue all prohibited medications ([Section 4.4.2](#)) at least 28 days before the start of Screening; this is the Washout Period.

If a prohibited medication must be tapered, tapering will be followed by discontinuation, and the discontinuation should last at least 28 days before the start of screening.

Patients will be instructed to continue their commercial pirfenidone during the Washout Period. After completing Washout, patients will enter Screening, which lasts up to 21 days; during Screening, patients will be evaluated for eligibility based on the inclusion

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and exclusion criteria. Patients not taking a prohibited medication will forgo Washout and directly enter Screening.

At screening, after eligibility criteria have been met, patients may be provided pirfenidone for the study and will be instructed on proper use. In this case, patients will be instructed to stop taking their commercial pirfenidone and start taking the study provided pirfenidone.

During Screening, patients on a stable dose of pirfenidone may return for the Baseline Visit (Study Day 1) as soon as eligibility has been confirmed. At this visit, they will have nintedanib added to the ongoing pirfenidone treatment. Nintedanib dosing will start at 100 mg once daily (QD) and be titrated to 150 mg BID over 15 days, as tolerated, according to the schedule provided in [Table 1](#).

The Sponsor will supply pirfenidone and nintedanib for use in the study; nintedanib will be supplied in 100 mg and 150 mg capsules to facilitate temporary dose reduction if required for the management of AEs.

Combination treatment will continue through Week 24, with monitoring by office visits and telephone contacts. Blood samples will be obtained from all patients for analysis of clinical laboratory values.

Patients will be encouraged to remain on stable doses of pirfenidone (1602–2403 mg/d) and nintedanib (200–300 mg/d) throughout the combination-treatment period, unless dosing is modified to manage an AE ([Section 4.3.2.5](#)). Patients will return to the clinic for a final Follow-up Visit 28–35 days after the completion of combination treatment.

If one or both study treatments are prematurely discontinued or interrupted for ≥ 28 consecutive days, nintedanib treatment will end as will the patient's participation in the study; whether commercial pirfenidone treatment continues will be left to the judgment of the Investigator. The patient will then return to the clinic as soon as possible (and ≤ 7 days after the decision to discontinue nintedanib) for an Early Discontinuation Visit.

In addition, 28–35 days after the decision to discontinue nintedanib, the patient will return for a final Follow-up Visit.

A patient diary will be used to record AEs, daily dosing adherence for both pirfenidone and nintedanib, and concomitant medication use from the screening visit to the final Follow-up Visit. Also, patients will receive a wallet card that provides important information relevant to study participation.

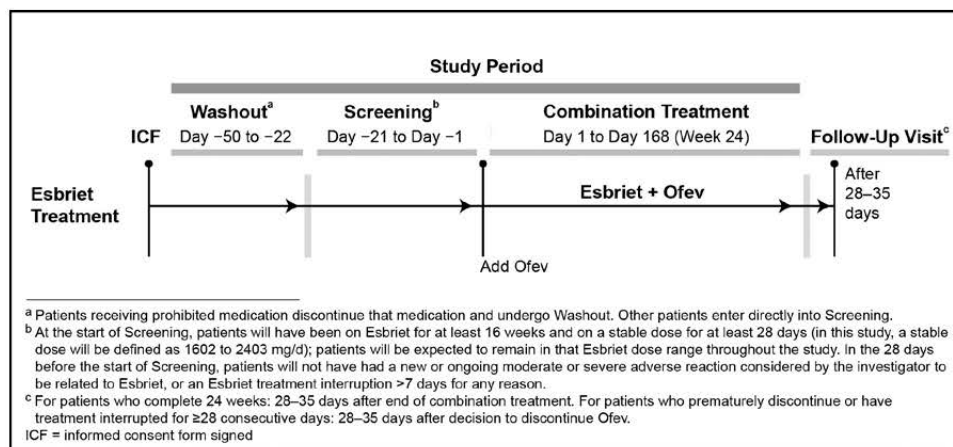
On completion of study participation, patients may be prescribed appropriate IPF treatment at the discretion of the treating physician.

An independent Data Monitoring Committee (iDMC) will review safety data and advise on study conduct at least three times during the study: when the first approximately 20 patients have completed 8 weeks of combination treatment or permanently discontinued one or both study treatments, when approximately 50% of the total patient group has completed 12 weeks of combination treatment or permanently discontinued one or both study treatments and when approximately 75% of the total patient group has completed 24 weeks of combination treatment or permanently discontinued one or both

study treatments. Additional ad hoc meetings or data reviews can be requested at any time by the iDMC or the Sponsor, if warranted.

A Schedule of Assessments is provided in [Appendix 1](#).

Figure 1: Design of Study



3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur in the 4th quarter of 2017.

Length of Study

The expected study length is up to 21 months

End of Study

January 2018

3.3 RATIONALE FOR STUDY DESIGN

The mechanism of action of pirfenidone in IPF has not been established ([Esbriet[®] UUSPI 2014](#)), while nintedanib is thought to act by inhibiting multiple RTKs and nRTKs ([Ofev[®] USPI 2014](#)). Because multiple co-activated pathways are involved in the pathogenesis of IPF, experts have suggested that targeted therapies may work better in combination ([Wuyts et al. 2014](#)). Furthermore, experience in other pulmonary diseases (e.g., asthma, chronic obstructive pulmonary disease, and pulmonary hypertension) has demonstrated the value of moving from monotherapy to combination therapy.

In certain patients with IPF who are tolerating pirfenidone, it is possible that physicians will choose to add nintedanib to explore the effect of combining two treatments that have different mechanisms of action. Considering the overlap in the GI and hepatic AEs associated with these two drugs, we believe that an essential first step in exploring pirfenidone/nintedanib combination treatment is to characterize its safety and tolerability using the doses recommended in the pirfenidone and nintedanib labels.

This prospective Phase 4 study will evaluate the safety and tolerability of 24 weeks of pirfenidone/nintedanib combination treatment in patients with IPF who are on a stable dose of pirfenidone with demonstrated tolerability.

This study is not designed to formally evaluate the efficacy of combination treatment - efficacy will only be assessed in an exploratory manner - nor is it designed to assess the safety and tolerability of adding pirfenidone to ongoing nintedanib treatment.

Refer to [Section 4.3.2](#) or the detailed dosing information.

3.3.1 Rationale for Pirfenidone and Nintedanib Dose and Schedule

In this study, nintedanib will be added to ongoing treatment with a stable dose of pirfenidone. Combination treatment will continue for 24 weeks, and the doses and treatment regimen will be as follows:

- In accordance with the pirfenidone prescribing information, the dose is 801 mg (i.e. three 267 mg capsules) TID, at the same times each day, taken with food (total dose, 2403 mg/d).
- In accordance with the nintedanib prescribing, dose is 150 mg BID, approximately 12 hours apart, at the same times each day, taken with food (total dose, 300 mg/d).

Patients will be encouraged to remain on stable doses of pirfenidone and nintedanib throughout the combination-treatment period, unless dosing is modified to manage an AE.

3.3.2 Rationale for Patient Population

The selected study population is that for which pirfenidone and nintedanib are licensed, matching the patient population in the Phase 3 program with pirfenidone. The Phase 3 program confirmed the efficacy of pirfenidone on slowing progression of disease as measured by FVC, however, this patient population might benefit from a combination treatment with another anti-fibrotic drug shown to be efficacious in IPF.

4. MATERIALS AND METHODS

4.1 PATIENTS

The study population will consist of males and females with IPF who meet the inclusion criteria.

4.1.1 Inclusion Criteria

Eligible patients for this study must meet the following criteria for study entry:

1. Written informed consent to participate in the study
2. Male or female, and age 40 through 80 years old at the start of Screening (inclusive).
3. At the start of Screening, on pirfenidone for at least 16 weeks and on a stable dose for at least 28 days (in this study, a stable dose will be defined as 1602–2403 mg/d); the dose must be expected to remain in that range throughout the study.

4. Documented diagnosis of IPF, per the Investigator per using the criteria of the 2011 ATS / ERS / JRS / ALAT guidelines
5. The value from pulmonary function test results (from documented pulmonary function laboratory reports) measured at screening visit as follows:
 - Percent predicted FVC \geq 50%.
 - Percent predicted DLco (or carbon monoxide transfer capacity converted to DLco) \geq 30%.
6. Able to understand the importance of adherence to the study treatment regimen and the study protocol, and willing to follow all study requirements, including the concomitant medication restrictions, throughout the study.
7. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of $< 1\%$ per year, during the treatment period and for at least 3 months after the final Follow-up Visit.
 - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
 - Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices.
 - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
 - Barrier methods must always be supplemented with the use of a spermicide.
8. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
 - With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least for at least 4 months after the final Follow-up Visit. Men must refrain from donating sperm during this same period.
 - With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least for at least 4 months after the final Follow-up Visit.
 - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Clinical evidence of any active infection which according to the judgment of the investigator may interfere with study conduct, measurement of pulmonary function, or impact the course of IPF.
2. In the 28 days before the start of Screening, any new or ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone, or an pirfenidone treatment interruption > 7 days for any reason.
3. Any condition that is likely to result in death in the 12 months after the start of Screening.
4. Lung transplantation anticipated in the 12 months after the start of Screening.
5. Any planned significant surgical intervention from the start of Screening through the final Follow-up Visit. This does not include minor surgical procedures (e.g., excision of a localized basal cell carcinoma).
6. Known hypersensitivity to the active substance or any excipient of either pirfenidone or nintedanib.
7. Any condition that, in the Investigator's judgment, might be significantly exacerbated by the known side effects associated with the administration of pirfenidone or nintedanib.
8. Mild (Child Pugh A), moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment.
9. Severe renal impairment (creatinine clearance < 30 mL/min by the Cockcroft-Gault calculation), including end-stage renal disease requiring dialysis.
10. History or risk of GI tract perforation.
11. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) in the 6 months before the start of Screening, including but not limited to, the following:
 - Unstable angina pectoris or myocardial infarction.
 - Congestive heart failure expected to require hospitalization during the study.
 - Uncontrolled clinically significant arrhythmias.
12. Electrocardiogram (ECG), with a heart-rate-corrected QT interval (corrected using Fridericia's formula, QTcF) \geq 500 ms at Screening, or a family or personal history of long QT syndrome.
13. Bleeding risk: genetic predisposition to bleeding, a hemorrhagic event in the 12 months before the start of Screening, or abnormal laboratory coagulation parameters. Patients who require fibrinolysis, full-dose therapeutic anticoagulation (e.g., vitamin K antagonists, dabigatran, heparin, hirudin), high-dose antiplatelet therapy, or other therapy that may substantially increase bleeding risk are excluded.

Note: the following are permitted: prophylactic low-dose heparin or heparin flush as needed for maintaining an indwelling intravenous device (e.g., enoxaparin 4000 IU SC per day), as well as prophylactic use of antiplatelet therapy (e.g., acetylsalicylic acid up to 325 mg/d, clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy).

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14. Use of strong CYP1A2 inhibitors (e.g., fluvoxamine, enoxacin) in the 28 days before the start of Screening.
15. Use of inhibitors of P-glycoprotein (e.g., ketoconazole, erythromycin) or CYP3A4 (e.g., ketoconazole, erythromycin) or their inducers (e.g., rifampicin, carbamazepine, phenytoin, St John's wort) in the 28 days before the start of Screening.
16. History of alcohol or substance abuse in the 2 years before the start of Screening.
17. Use of any tobacco product in the 12 weeks before the start of Screening, or an unwillingness to abstain from their use through the final Follow-up Visit.
18. In the judgment of the Investigator, not a suitable candidate for enrollment, or unlikely or unable to comply with the requirements of this study.
19. Use of any investigational therapy in a clinical study protocol in the 28 days before the start of Screening
20. Pregnancy or lactation.
21. Hypersensitivity to peanuts.
22. Hypersensitivity to soy.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

This is a single-group, open-label, non-randomized, interventional, safety and tolerability study, and all patients will receive the same study treatment (combination treatment with pirfenidone and nintedanib) during the study period.

4.3 STUDY TREATMENT

There are two investigational medicinal products (IMP) in this study, pirfenidone and nintedanib.

4.3.1 Formulation, Packaging and Handling

4.3.1.1 Pirfenidone

The chemical name of pirfenidone is 5-methyl-1-phenyl-2-(1H)-pyridone.

Pirfenidone (pirfenidone 267 mg) will be supplied as white, hard gelatin capsules printed with "267 mg" in brown ink.

Each pirfenidone capsule contains 267 mg of pirfenidone, and the following inactive ingredients:

- Inactive ingredients: microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate
- Capsule shell: gelatin, titanium dioxide, brown printing ink (includes shellac, iron oxide black, iron oxide red, iron oxide yellow, propylene glycol, ammonium hydroxide)

Store pirfenidone according to the IMP label. Keep the bottle tightly closed.

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4.3.1.2 Nintedanib

Nintedanib will be added to the ongoing pirfenidone treatment on Study Day 1. The recommended dose is 150 mg BID, approximately 12 hours apart, at the same times each day, taken with food (total dose, 300 mg/d). Nintedanib doses of > 300 mg/d are not recommended for any patient.

Nintedanib is presented as the ethanesulfonate salt (esylate), with the chemical name 1H-Indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl]-amino]phenyl]amino]phenylmethylene]-2-oxo-,methyl ester, (3Z)-, ethanesulfonate (1:1).

Nintedanib will be supplied as follows:

- 100 mg capsules: peach, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and “100”
- 150 mg capsules: brown, opaque, oblong, soft capsules imprinted in black with the Boehringer Ingelheim company symbol and “150”

Each nintedanib capsule contains 100 or 150 mg of nintedanib, equivalent to 120.40 or 180.60 mg nintedanib ethanesulfonate, respectively. The inactive ingredients of nintedanib are as follows:

- Fill material: triglycerides, hard fat, lecithin
- Capsule shell: gelatin, glycerol, titanium dioxide, red ferric oxide, yellow ferric oxide, black ink

Store nintedanib according to the IMP label. Protect from exposure to high humidity and avoid excessive heat. If repackaged, use U.S. Pharmacopeial Convention (USP) tight container. Keep out of reach of children.

4.3.2 Dosage, Administration and Compliance

4.3.2.1 Pirfenidone

Pirfenidone – The recommended dose of pirfenidone is 801 mg (i.e., three 267 mg capsules) TID, at the same times each day, taken with food (total dose, 2403 mg/d). Pirfenidone doses > 2403 mg/d are not recommended for any patient.

In this study, patients will be on a stable pirfenidone dose (as specified in the inclusion criteria) before nintedanib treatment starts, and a stable pirfenidone dose will be defined as 1602–2403 mg/d. Furthermore, patients' pirfenidone doses will be expected to remain within that pirfenidone dose range throughout the study, unless dosing is modified to manage an AE ([Section 4.3.2.5](#)).

Guidelines for dosage modification and treatment interruption or discontinuation are provided in [Section 4.3.2.5](#) to [Section 4.3.2.7](#).

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF

4.3.2.2 Nintedanib

Nintedanib will be added to the ongoing pirfenidone treatment on Study Day 1. The recommended dose is 150 mg BID, approximately 12 hours apart, at the same times each day, taken with food.

Nintedanib dosing will start at 100 mg QD and be titrated to 150 mg BID over 15 days, as described in Table 1. In this study, a stable dose of nintedanib will be defined as 200–300 mg/d, and patients' nintedanib doses will be expected to remain within that dose range throughout the study, unless dosing is modified to manage an AE (Section 4.3.2.5). Patients unable to tolerate nintedanib at a dose of 200 mg/d will be withdrawn from the study.

Table 1 Schedule for Initiation of Nintedanib Treatment

Day (relative to the first dose of nintedanib)	Nintedanib Dosage (as tolerated)
1 through 7	one 100 mg capsule QD, with food
8 through 14	one 100 mg capsule BID, with food
15, forward	one 150 mg capsule BID, with food

BID = two times daily; QD = once daily

4.3.2.3 Precautionary Measures during Treatment with Pirfenidone

Exposure to sunlight (including indirect light, sunlamps, and tanning beds) should be avoided or minimized during pirfenidone treatment due to the possibility of photosensitivity reactions or rash.

Patients should be instructed to use sunscreens that have a sun protection factor (SPF) ≥ 50 as well as protection against ultraviolet A (UV-A) and ultraviolet B (UV-B) radiation, and also to wear clothing that protects against sun exposure and avoid concomitant medications known to cause photosensitivity reactions, if possible.

All doses of pirfenidone are to be taken with food to reduce the likelihood of GI symptoms or dizziness. Dose titration when pirfenidone is restarted after a treatment interruption is intended to enhance tolerability.

4.3.2.4 Missed Doses

If a patient misses a scheduled dose of pirfenidone and/or nintedanib, the dose should be skipped. Regular dosing will resume with the next scheduled dose. The patient should not take any extra doses to make up for missed doses.

4.3.2.5 Dose Modification or Discontinuation

The Investigator will be responsible for monitoring patients as frequently as clinically indicated for treatment-emergent AEs (TEAEs) or other toxicities, and for doing so in a manner consistent with the instructions in the labels for pirfenidone, nintedanib, and any other medications used to treat a study patient.

The Investigator may contact the Medical Monitor or designee to discuss dose modification or discontinuation of study treatment. All TEAEs and toxicities will be followed according to procedures in this protocol.

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If a patient experiences a clinically significant TEAE or toxicity, treatment of symptoms and/or temporary dose reduction, interruption, or discontinuation of study treatment should be considered. All changes in dosing will be recorded by the patient in the patient diary and by the study center in the electronic eCRF.

If a patient is hospitalized for any reason, the Investigator should consider continuing combination treatment if appropriate. If the patient is hospitalized at an institution that is not affiliated with the study center, the Investigator is encouraged to discuss study participation with the treating physician at the earliest possible time. All records pertaining to the hospitalization should be obtained by the study center.

The sections below identify events that require discontinuation of study treatment, and provide guidance for modifying doses, restarting treatment after an interruption of < 28 consecutive days, and managing study treatment in the presence of elevated liver test results, a photosensitivity reaction/rash, nausea/vomiting/diarrhea, a clinically significant vascular event, GI perforation, or QTcF prolongation.

4.3.2.6 Dose Modification

The Investigator is responsible for making decisions about treatment discontinuation, temporary dose modification (i.e., reduction or interruption of one or both study treatments), and whether treatment will be restarted after an interruption of < 28 consecutive days, using the guidance provided in this protocol.

The Medical Monitor or designee will be available to discuss the management of TEAEs and dose modification as needed, and Investigators may contact the Medical Monitor or designee for consultation or to request clarification of the guidance in this protocol.

Dose modification will be managed as follows:

- If dose modification is required for elevated liver test results; a photosensitivity reaction or rash; nausea, vomiting, or diarrhea; a clinically significant vascular event; GI perforation; or QTcF prolongation, follow the guidance below
- If dose modification is required for other TEAEs, the nintedanib dose will be modified as an initial step. Whether pirfenidone treatment is maintained, dose-reduced, or interrupted will be left to the clinical judgment of the Investigator. After study inclusion (Screening day -21) investigators should aim to achieve a pirfenidone target dose 1602–2403 mg/d. Dose modifications i.e. reductions due to side effects can be made at any upon the investigator's discretion.

After resolution of the event or sufficient improvement, the dose of study treatment can be increased to the target dose or treatment can be restarted at the discretion of the Investigator, if any treatment interruption was < 28 consecutive days. If treatment is restarted, that should be done as described in [Table 2](#).

4.3.2.7 Restarting Study Treatment

After a treatment interruption of < 28 consecutive days, study treatment can be restarted, at the discretion of the Investigator, as described below ([Table 2](#)). After an interruption of ≥ 28 consecutive days, study treatment will not be restarted and the patient will be withdrawn from the study.

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Table 2 Restarting Study Treatment after an Interruption of < 28 Consecutive Days

Duration of Interruption: < 14 days (consecutive)	
Only Pirfenidone	<p>If nintedanib had been titrated to highest tolerated dose:</p> <ul style="list-style-type: none"> – restart pirfenidone at the previous dose or a reduced dose, as clinically appropriate – retitrate to 801 mg TID, as tolerated [a] <p>If nintedanib had not been titrated to highest tolerated dose:</p> <ul style="list-style-type: none"> – first retitrate pirfenidone to 801 mg TID, as tolerated – then resume titration of nintedanib to 150 mg BID, as tolerated [a]
Only Nintedanib	<ul style="list-style-type: none"> – Restart at the previous dose or a reduced dose, as clinically appropriate – retitrate to 150 mg BID, as tolerated [a]
Both Pirfenidone and Nintedanib	<p>Pirfenidone</p> <ul style="list-style-type: none"> – first restart pirfenidone at the previous dose or a reduced dose, as clinically appropriate – retitrate to 801 mg TID, as tolerated [a] <p>Nintedanib</p> <ul style="list-style-type: none"> – after the patient has been on the highest tolerated pirfenidone dose for at least 7 days, restart nintedanib at the previous dose or a reduced dose, as clinically appropriate – retitrate nintedanib to 150 mg BID, as tolerated [a]
Duration of Interruption: 14 to < 28 days (consecutive)	
Only Pirfenidone	<p>If nintedanib had been titrated to highest tolerated dose:</p> <ul style="list-style-type: none"> – retitrate pirfenidone according to the schedule in Table 3 <p>If nintedanib had not been titrated to highest tolerated dose:</p> <ul style="list-style-type: none"> – first retitrate pirfenidone according to the schedule in Table 3 – then resume titration of nintedanib to 150 mg BID, as tolerated [b]
Only Nintedanib	<ul style="list-style-type: none"> – Restart at the previous dose or a reduced dose, as clinically appropriate – retitrate over 14 days to 150 mg BID, as tolerated [b].
Both Pirfenidone and Nintedanib	<p>Pirfenidone</p> <ul style="list-style-type: none"> – first retitrate pirfenidone according to the schedule in Table 3 <p>Nintedanib</p> <ul style="list-style-type: none"> – after the patient has been on the highest tolerated dose of pirfenidone for at least 7 days, restart nintedanib at the previous dose or a reduced dose, as clinically appropriate – retitrate nintedanib over 14 days to 150 mg BID, as tolerated [b]

BID = twice daily; TID = three times daily

- a. Pirfenidone and nintedanib dose-escalation schedules and the duration of the retitration periods will be determined by the Investigator. For nintedanib, the dose titration schedule used at the start of treatment (Table 1) can be used for retitration, if clinically appropriate.
- b. Nintedanib dose-escalation schedule will be determined by the Investigator. For nintedanib, the dose titration schedule used at the start of treatment (Table 1) can be used for retitration, if clinically appropriate.

If pirfenidone treatment is restarted after an interruption of 14 to < 28 consecutive days, it will be retitrated as shown in Table 3.

Table 3 Schedule for Pirfenidone Retitration after an Interruption of 14 to < 28 Consecutive Days

Day (relative to restart of pirfenidone treatment)	Pirfenidone Dosage (as tolerated)
1 through 7	1 capsule TID, with food
8 through 14	2 capsules TID, with food
15, forward	3 capsules TID, with food

TID = three times daily

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 4.3.2.5 to Section 4.3.2.7.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic eCRF. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (pirfenidone, nintedanib) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Pirfenidone and/or Nintedanib

Currently, the Sponsor does not have definitive plans yet to provide pirfenidone or nintedanib or any other study treatments or interventions to patients who have completed the study, in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

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4.4 CONCOMITANT THERAPY, PROHIBITED FOOD AND ADDITIONAL RESTRICTIONS

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from 28 days before the start of Screening and during the study. All such medications should be reported to the Investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

All medical therapies necessary to treat the patient's comorbidities and which are not listed below in Section 4.4.2 are permitted in this study.

4.4.2 Prohibited Therapy

The following medications will be prohibited in the 28 days before the start of Screening and during the study:

- Any cytotoxic, immunosuppressive, cytokine-modulating, or receptor-antagonist agent, including but not limited to azathioprine, bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene antagonists, methotrexate, mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, TNF- α inhibitors, N-acetylcysteine (NAC, imatinib mesylate, Interferon gamma-1b and tyrosine kinase inhibitors, other than nintedanib.
- Strong CYP1A2 inhibitors (e.g., fluvoxamine, enoxacin)
- Inhibitors of P-glycoprotein (e.g., ketoconazole, erythromycin) or CYP3A4 (e.g., ketoconazole, erythromycin), or their inducers (e.g., rifampicin, carbamazepine, phenytoin, phenytoin, St John's wort).
- Fibrinolytic therapy, full-dose therapeutic anticoagulation (e.g., vitamin K antagonists, dabigatran, heparin, hirudin), high-dose antiplatelet therapy, or other therapy that may substantially increase bleeding risk.
- Medications that are specifically being used for the treatment of IPF, including but not limited to angiotensin converting enzyme inhibitors, colchicine, corticosteroids, heparin, warfarin, and HMG-CoA reductase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication.
- Any investigational therapy in a clinical study.
- Because moderate inhibitors of CYP1A2 (e.g., ciprofloxacin) increase systemic exposure of pirfenidone ([Esbriet® USPI 2014](#)), if ciprofloxacin is administered it should be limited to 250 or 500 mg QD, and the patient should be monitored closely for AEs. Ciprofloxacin should not be used at a dose > 500 mg/d during the study.

The above lists of medications are not necessarily comprehensive. Thus, the Investigator should consult the prescribing information for any concomitant medication as well as the Internet references provided below when determining whether a certain medication is metabolized by or strongly inhibits or induces CYP1A2. In addition, the

Investigator should contact the Medical Monitor if questions arise regarding medications not listed above.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

<http://medicine.iupui.edu/clinpharm/ddis/table.aspx>

The following will be permitted:

- prophylactic low-dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g., enoxaparin 4000 IU SC per day)
- prophylactic use of antiplatelet therapy (e.g., acetylsalicylic acid up to 325 mg/d, clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy).

4.4.3 Prohibited Food

The consumption of grapefruit juice, soy products and soy lecithin containing products will be prohibited from the start of Screening through the Week 24 or Early Discontinuation Visit.

4.4.4 Additional Restrictions

The use of any tobacco product will be prohibited from 12 weeks before the start of Screening through the final Follow-up Visit.

4.5 STUDY ASSESSMENTS

4.5.1 Schedule of Study Assessments

The schedule for all study assessments and procedures is in [Appendix 1](#). At the discretion of the Investigator, a planned telephone assessment can be converted to an office visit and additional office visits can be scheduled. The results of all assessments and procedures will be documented in the patient's medical record and in study documentation, including the eCRF.

4.5.1.1 Washout of Prohibited Medication (Day -50 to Day -22)

Written informed consent must be obtained before any study-mandated assessments or procedures are performed, including discontinuing prohibited medication. Inclusion and Exclusion criteria are to be carefully checked.

Any patient identified for the study must discontinue all prohibited medications ([Section 4.4.2](#)) at least 28 days before the start of Screening; this is the Washout Period. Patients will be instructed to continue their commercial pirfenidone during the Washout Period. If a prohibited medication must be tapered, tapering must start early enough that the patient has discontinued the medication 28 days before the start of Screening.

Before entering a patient into the Washout Period, all relevant medical history, diagnostic findings, measures of disease severity, and the inclusion/exclusion criteria ([Section 4.1](#)) should be reviewed to evaluate the patient's suitability for the study. If the patient is deemed eligible to participate, the informed consent form must be signed prior to the patient being asked to stop the prohibited medication.

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The Investigator must explain to the patient that entry into the study is not guaranteed.

4.5.1.2 Screening Period (Day –21 to Day –1)

Screening assessments and procedures can be conducted on different days within the Screening Period if convenient. Screening tests can be repeated to ensure eligibility. As soon as patients have completed the washout of any prohibited medications, are on a stable dose of pirfenidone, have completed all of the assessments for the screening period and have met all other eligibility criteria, they may return for the Baseline Visit (Study Day 1).

The following assessments and procedures will be conducted during the Screening Period:

- Obtain written informed consent, if it was not obtained at Washout.
- Obtain a complete medical history, including the following:
 - Systems review
 - Review of concomitant medications
 - Review of historical data, including any prior high-resolution computed tomography scans, pulmonary function tests, and surgical lung biopsy data, if available
 - Review of events that occurred in the 28 days before the start of Screening: A patient is not eligible if he or she had either a new or ongoing moderate or severe adverse reaction considered by the Investigator to be related to pirfenidone
- Review pirfenidone treatment history: Review dose and frequency of commercial pirfenidone with patient to assess for compliance. At the start of Screening, the patient is to have been on pirfenidone for at least 16 weeks and on a stable dose (1602–2403 mg/d) for at least 28 days; the dose must be expected to remain within that range throughout the study. Also, there must be no > 7 day treatment interruption for any reason in the 28 days before the start of Screening.
- Ensure that patient has not participated in another Clinical Study within < 28 days.
- Document the diagnosis of IPF
- Perform a complete physical examination, including vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure height (cm) and body weight (kg)
- Obtain a 12-lead ECG (before samples for laboratory assessments are obtained). Use of short-acting bronchodilators is prohibited in the 6 hours before the ECG test, and use of long-acting bronchodilators is prohibited in the 24 hours before the test.
- Perform the DLco test before or at least 30 minutes after the last puff of a short-acting bronchodilator. For a pre-bronchodilator measurement, use of short-acting bronchodilators is prohibited in the 6 hours before the start of the test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.
- Perform spirometry (FVC) and forced expiratory volume at 1 second [FEV1] tests before and approximately 30 minutes after short-acting bronchodilator administration.

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Use of short-acting bronchodilators is prohibited in the 6 hours before the start of the pre-bronchodilator test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.

- Obtain blood samples for laboratory assessments: hematology, serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula), C-reactive protein (CRP) and a serum pregnancy test for women of childbearing potential.
- Review the inclusion and exclusion criteria to determine whether the patient is eligible for the study.
- Once eligibility, to this point, has been established, dispense study-supplied pirfenidone. Explain to patient that they must stop taking their commercial Esbriet and only take study-supplied pirfenidone while on the study and that they will be instructed when to resume their commercial Esbriet. Instruct the patient on proper dosing.
- Provide the patient with the patient diary, and instruct the patient how to record information properly.
- Obtain percent predicted FVC, FEV1 and percent predicted DLco or measurements from the 12 months before the start of Screening, if available (must be from documented pulmonary function laboratory reports).

4.5.1.3 Baseline Visit (Day 1, office visit)

The following assessments and procedures will be conducted on Day 1, the first day of nintedanib treatment:

- Review the inclusion and exclusion criteria, including criteria related to concomitant medications, to confirm that the patient remains eligible for the study.
- If patient is taking study pirfenidone:
 - Collect unused pirfenidone capsules and empty bottles to monitor for dosing adherence. Assess pirfenidone dosing adherence since the Screening Visit.
- If patient is taking commercial Esbriet:
 - Assess pirfenidone ask patient if he/she has taken their medication.
- Review the patient diary for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").
- If patient is not eligible to enter the study, instruct patient to resume their commercial Esbriet and at what dose they should resume.
- Obtain a directed medical history, reviewing the period since the Screening Visit.
- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure body weight (kg).

- Obtain a 12-lead ECG (before samples for laboratory assessments are obtained). Use of short-acting bronchodilators is prohibited in the 6 hours before the ECG test, and use of long-acting bronchodilators is prohibited in the 24 hours before the test.
- Perform the DLco test before or at least 30 minutes after the last puff of a short-acting bronchodilator. For a pre-bronchodilator measurement, use of short-acting bronchodilators is prohibited in the 6 hours before the start of the test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.
- Perform spirometry (FVC, FEV1) tests before and approximately 30 minutes after short-acting bronchodilator administration. Use of short-acting bronchodilators is prohibited in the 6 hours before the start of the pre-bronchodilator test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.
- Obtain blood samples for laboratory assessments: hematology, serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula), CRP and a serum pregnancy test for women of childbearing potential
- Collect samples for biomarker assessment
- Explain to the patient the plan for obtaining the Day 7 blood samples (refer to [Section 4.5.7.1](#) for additional information):
 - If the Day 7 samples will not be drawn at the Investigator's study center, provide the patient with a laboratory kit and shipping supplies, explain their purpose, and instruct the patient to have the samples drawn on Day 7 (\pm 3 days).
 - If the samples are to be drawn at the Investigator's study center, instruct the patient to return to the center on Day 7 (\pm 3 days).
- Perform [REDACTED] questionnaire.
- Provide the patient with the wallet card that has important information relevant to study participation.
- Dispense pirfenidone and nintedanib for use in the study, and instruct the patient on proper dosing.
- Nintedanib dosing will start at 100 mg QD and be titrated to 150 mg BID over 15 days, as tolerated, according to the schedule in [Table 1](#).

4.5.1.4 Day 7 \pm 3 days (Week 1, telephone contact)

The following assessments will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Interview the patient to assess for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").
- Remind the patient to have blood samples drawn on Day 7 (\pm 3 days).

4.5.1.5 Day 14 ± 3 days (Week 2, office visit)

The following assessments and procedures will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Review the patient diary for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").
- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure body weight (kg).
- Obtain blood samples for laboratory assessments: hematology and serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula) and CRP.
- Explain to the patient the plan for obtaining the Day 21 blood samples (refer to [Section 4.5.7.1](#) for additional information):
 - If the Day 21 samples will not be drawn at the Investigator's study center, provide the patient with a laboratory kit and shipping supplies, explain their purpose, and instruct the patient to have the samples drawn on Day 21 (± 3 days).
 - If the samples are to be drawn at the Investigator's study center, instruct the patient to return to the center on Day 21 (± 3 days).

4.5.1.6 Day 21 ± 3 days (Week 3, telephone contact)

The following assessments will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Interview the patient to assess for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").
- Remind the patient to have blood samples drawn on Day 21 (± 3 days).

4.5.1.7 Day 28 ± 3 days (Week 4, office visit)

The following assessments and procedures will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Review the patient diary for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").
- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.

- Measure body weight (kg).
- Perform a urine pregnancy test for women of childbearing potential. If urine pregnancy test is positive, a serum pregnancy test must be drawn for confirmation.
- Obtain blood samples for laboratory assessments: hematology, serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula) and CRP.
- Collect samples for biomarker assessment

4.5.1.8 Day 42 ± 7 days (Week 6, telephone contact)

The following assessments will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Interview the patient to assess for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").

4.5.1.9 Day 56 ± 7 days (Week 8, office visit)

The following assessments and procedures will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Review the patient diary for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").
- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure body weight (kg).
- Perform a urine pregnancy test for women of childbearing potential. If urine pregnancy test is positive, a serum pregnancy test must be drawn for confirmation.
- Obtain blood samples for laboratory assessments: hematology and serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula) and CRP.
- Collect unused pirfenidone and nintedanib capsules and empty bottles to monitor for dosing adherence. Dispense pirfenidone and nintedanib for use in the study, and instruct the patient on proper dosing.

4.5.1.10 Day 70 ± 7 days (Week 10, telephone contact)

The following assessments will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Interview the patient to assess for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the diary, doing so

with minimal connotations (e.g., "Have you had any health problems since your last visit?").

4.5.1.11 Day 84 ± 7 days (Week 12, office visit)

The following assessments and procedures will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Review the patient diary for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").
- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure body weight (kg).
- Perform the DLco test before or at least 30 minutes after the last puff of a short-acting bronchodilator. For a pre-bronchodilator measurement, use of short-acting bronchodilators is prohibited in the 6 hours before the start of the test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.
- Perform spirometry (FVC) tests before and approximately 30 minutes after short-acting bronchodilator administration. Use of short-acting bronchodilators is prohibited in the 6 hours before the start of the pre-bronchodilator test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.
- Perform a urine pregnancy test for women of childbearing potential. If urine pregnancy test is positive, a serum pregnancy test must be drawn for confirmation.
- Obtain blood samples for laboratory assessments: hematology and serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula) and CRP.

4.5.1.12 Day 98 ± 7 days (Week 14, telephone contact)

The following assessments will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Interview the patient to assess for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").

4.5.1.13 Day 112 ± 7 days (Week 16, office visit)

The following assessments and procedures will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Review the patient diary for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with

minimal connotations (e.g., "Have you had any health problems since your last visit?").

- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure body weight (kg).
- Perform a urine pregnancy test for women of childbearing potential. If urine pregnancy test is positive, a serum pregnancy test must be drawn for confirmation.
- Obtain blood samples for laboratory assessments: hematology and serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula) and CRP.
- Collect unused pirfenidone and nintedanib capsules and empty bottles to monitor for dosing adherence. Dispense pirfenidone and nintedanib for use in the study, and instruct the patient on proper dosing.

4.5.1.14 Day 126 ± 7 days (Week 18, telephone contact)

The following assessments will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Interview the patient to assess for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").

4.5.1.15 Day 140 ± 7 days (Week 20, office visit)

The following assessments and procedures will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Review the patient diary for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with minimal connotations (e.g., "Have you had any health problems since your last visit?").
- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure body weight (kg).
- Perform a urine pregnancy test for women of childbearing potential. If urine pregnancy test is positive, a serum pregnancy test must be drawn for confirmation.
- Obtain blood samples for laboratory assessments: hematology and serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula) and CRP.

4.5.1.16 Day 168 ± 7 days (Week 24, office visit)

The following assessments and procedures will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Review the patient diary for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with minimal connotations (e.g., “Have you had any health problems since your last visit?”).
- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure body weight (kg).
- Obtain a 12-lead ECG (before samples for laboratory assessments are obtained). Use of short-acting bronchodilators is prohibited in the 6 hours before the ECG test, and use of long-acting bronchodilators is prohibited in the 24 hours before the test.
- Perform the DLco test before or at least 30 minutes after the last puff of a short-acting bronchodilator. For a pre-bronchodilator measurement, use of short-acting bronchodilators is prohibited in the 6 hours before the start of the test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.
- Perform spirometry (FVC) tests before and approximately 30 minutes after short-acting bronchodilator administration. Use of short-acting bronchodilators is prohibited in the 6 hours before the start of the pre-bronchodilator test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.
- Obtain blood samples for laboratory assessments: hematology, serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula), CRP and a serum pregnancy test for women of childbearing potential.
- Collect samples for biomarker assessment
- Perform [REDACTED] questionnaire.
- Collect unused pirfenidone and nintedanib capsules and empty bottles to monitor for dosing adherence.
- Instruct patient to resume their commercial Esbriet and at what dose they should resume.

4.5.1.17 Follow-up Visit, after 28–35 days (office visit)

Patients who complete 24 weeks of combination treatment will return to the clinic for the final Follow-up Visit 28–35 days after the completion of combination treatment.

Patients who prematurely discontinue treatment or have a treatment interruption of ≥ 28 consecutive days will first return to the clinic for an Early Discontinuation Visit (Section 4.3.2.5 and Section 4.6.1) and then return for the final Follow-up Visit 28–35 days after the decision to discontinue nintedanib.

The following assessments and procedures will be conducted at the final Follow-up Visit:

- Obtain a directed medical history, reviewing the period since the preceding visit.

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- Review the patient diary for AEs and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with minimal connotations (e.g., “Have you had any health problems since your last visit?”).
- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure body weight (kg).
- Obtain a 12-lead ECG (before samples for laboratory assessments are obtained). Use of short-acting bronchodilators is prohibited in the 6 hours before the ECG test, and use of long-acting bronchodilators is prohibited in the 24 hours before the test.
- Obtain blood samples for laboratory assessments: hematology, serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula), CRP and a serum pregnancy test for women of childbearing potential.
- Collect the patient diary.

4.5.1.18 Early Discontinuation Visit, conducted as soon as possible and ≤ 7 days after decision to discontinue nintedanib (office visit)

If a patient prematurely discontinues combination treatment or has a treatment interruption of ≥ 28 consecutive days, the patient will return to the clinic as soon as possible (and ≤ 7 days after the decision to discontinue nintedanib) for the Early Discontinuation Visit. If the patient is unable to return to the study center in the 7 days after the decision to discontinue nintedanib, the center will call the patient to review medical history and will send the patient a laboratory kit and shipping supplies so that the required blood samples can be drawn at a site closer to the patient's location (i.e., another study center, a commercial laboratory or by a home nursing agency); the Early Discontinuation Visit should then be scheduled as soon as possible. The patient will also return for the final Follow-up Visit 28–35 days after the decision to discontinue nintedanib.

The following assessments and procedures will be conducted:

- Obtain a directed medical history, reviewing the period since the preceding visit.
- Review the patient diary for AEs, dosing adherence, and concomitant medications. Inquire for AEs that may not have been recorded in the patient diary, doing so with minimal connotations (e.g., “Have you had any health problems since your last visit?”).
- Perform a complete physical examination, including vital signs (BP, HR, RR, and body temperature; to be performed before laboratory assessments). BP and HR are obtained sitting, after resting for 5 minutes.
- Measure body weight (kg).
- Obtain a 12-lead ECG (before samples for laboratory assessments are obtained). Use of short-acting bronchodilators is prohibited in the 6 hours before the ECG test, and use of long-acting bronchodilators is prohibited in the 24 hours before the test.
- Perform the DLco test before or at least 30 minutes after the last puff of a short-acting bronchodilator. For a pre-bronchodilator measurement, use of short-acting

bronchodilators is prohibited in the 6 hours before the start of the test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.

- Perform spirometry (FVC) tests before and approximately 30 minutes after short-acting bronchodilator administration. Use of short-acting bronchodilators is prohibited in the 6 hours before the start of the pre-bronchodilator test. Use of long-acting bronchodilators is prohibited in the 24 hours before the start of the test.
- Obtain blood samples for laboratory assessments: hematology, serum chemistry (including creatinine clearance rate, calculated using the Cockcroft-Gault formula), CRP and a serum pregnancy test for women of childbearing potential.
- Collect samples for biomarker assessment
- Perform [REDACTED] questionnaire.
- Collect unused pirfenidone and nintedanib capsules and empty bottles.
- Instruct patient to resume their commercial Esbriet and at what dose they should resume, if applicable.

4.5.1.19 Unscheduled Visits

The Investigator will be responsible for monitoring AEs and other toxicities.

Any follow-up to monitor patient safety that is performed outside of the scheduled visits will be recorded as an Unscheduled Visit. Unscheduled Visits can occur at any time, based on clinical need. The assessments and procedures conducted during the visit will be at the discretion of the Investigator. If there are additional clinical laboratory assessments, they should be obtained through the central laboratory.

4.5.1.20 Patients Lost to Follow-up

If a patient misses a visit and is not responding to telephone calls from the study center (all attempts to contact the patient should be documented), the center will need to take additional actions to locate the patient. The center will make at least two attempts to contact the patient by telephone and two additional attempts to contact the patient's emergency contact. If these attempts are not successful, a registered letter will be sent to the last known address of the patient. If this is not successful, as a last resort, the center will check the national death registries, where approved by regulatory authorities and available. If this is unsuccessful, the patient will be considered lost to follow-up.

Please see [Appendix 1](#) for the schedule of assessments performed during the study.

4.5.2 Informed Consent Forms and Screening Log

The Investigator or designee is responsible for the content of the informed consent form (ICF), but the content must be approved by the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and the Sponsor or its designee. The content of the informed consent must comply with Food and Drug (FDA) regulations (21 CFR 31.25) and the International Conference on Harmonisation (ICH) document "Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance," dated June 1996. It should also include any additional information required by local laws relating to institutional review.

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The Investigator is responsible for obtaining informed consent from each patient participating in the study. If there are amendments to the informed consent, patients should be re-consented in a timely fashion. All pertinent aspects of the study must be explained to the patient before he or she signs the ICF. Informed consent must be obtained from the patient before any Screening activity or treatment is undertaken that is not part of routine care. This includes, but is not limited to, the performance of diagnostic or therapeutic procedures, the tapering and/or discontinuation of any prohibited medications and the administration of the first dose of study supplied pirfenidone and/or nintedanib.

Before a patient's participation in the study, the written ICF should be signed and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. The informed consent document must be in a language understandable to the study patient or to his or her representative. The Investigator is responsible for keeping this document in a secure place.

A signed and dated copy of the ICF must be given to the person signing the document.

4.5.3 Medical History and Demographic Data

Medical history includes clinically significant diseases (surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the patient within 90 days prior to the Screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

A directed medical history will include the following:

- AEs
- Concomitant medications
- Dosing adherence
- Hospitalizations
- Inquiry regarding compliance with protocol requirements for contraceptive use (for women of childbearing potential, and sexually active men with partners of childbearing potential) and avoidance of tobacco products ([Section 4.4.4](#))
- Inquiry to determine whether patient is aware of being pregnant (for women of childbearing potential)

4.5.4 Physical Examinations

Complete physical examinations will include weight (kg) and vital signs (i.e. resting BP, resting HR, RR, and body temperature); in addition, at Screening, the examination will include height (cm).

If clinically significant abnormalities are observed in a physical examination performed on or before Day 1, they will be reported in the patient's medical history. If clinically

significant abnormalities are observed after Day 1, the Investigator will decide if they are new AEs.

4.5.5 Vital Signs

Vital signs will include measurements of pulse rate, respiratory rate, body temperature and systolic and diastolic BPs while the patient is in a seated position, after resting for 5 minutes.

4.5.6 Other Disease-Specific Assessments

Percent predicted FVC, FEV1 and percent predicted DLco will be considered additional disease assessments in this study.

All equipment, procedures, and personnel qualifications for the assessment of lung function will be based on the recommendations of the ATS ([American Thoracic Society 2005](#)):

FVC and FEV1 will be measured before and approximately 30 minutes after administration of approximately 360 µg of albuterol (4 actuations of 90 µg/actuation) or approximately 400 µg of salbutamol (4 actuations of 100 µg/actuation) from a metered-dose inhaler. Use of short-acting bronchodilators will be prohibited in the 6 hours before the start of the pre-bronchodilator test. Use of long-acting bronchodilators will be prohibited in the 24 hours before the start of the test.

DLco will be measured before or at least 30 minutes after the last puff of a short-acting bronchodilator. For a pre-bronchodilator measurement, use of short-acting bronchodilators will be prohibited in the 6 hours before the start of the test. Use of long-acting bronchodilators will be prohibited in the 24 hours before the start of the test.

4.5.7 Laboratory Samples

Instructions for collection and shipping of blood samples are in the Central Laboratory Manual.

4.5.7.1 Routine Clinical Laboratory Tests

A central laboratory will be used for the following assessments:

- Hematology (complete blood count with haemoglobin, white blood cell count, red blood cell count, haematocrit, platelet count and automated differential)
- Serum chemistry (albumin, alkaline phosphatase, ALT, AST, direct bilirubin, total bilirubin, calcium, cholesterol, creatine kinase, creatinine, triglycerides, gamma-glutamyl transferase, glucose, lactic dehydrogenase, magnesium, phosphorus, potassium, sodium, urea nitrogen, uric acid, and amylase)
- Quantitative high-sensitivity
- Serum pregnancy tests for women of childbearing potential (also, on Day 1, the study center will perform a urine pregnancy test for women of childbearing potential)
- Creatinine clearance rate will be calculated using the Cockcroft-Gault formula.

The Investigator will review laboratory test results and assess the clinical significance of any analyte that is outside the normal range. Safety laboratory data will be reviewed, initialled, and dated by the Principal Investigator (PI) or designee within 24 hours of receipt. It will be the Investigator's responsibility to perform laboratory assessments more frequently if clinically indicated. The central laboratory should be used for the analysis unless there is an emergency.

Blood samples for the Day 7 and Day 21 laboratory tests (i.e., weeks with no office visit) will be obtained as follows. If the blood samples cannot be drawn at the Investigator's study center, the patient will have it drawn at a site closer to his or her residence (i.e., another study center, commercial laboratory or by a home nursing agency). If the samples will not be drawn at the Investigator's study center, the patient will be given a laboratory kit and shipping supplies that will be used to draw the samples and send them to the central laboratory for analysis. Before giving the kit and shipping supplies to the patient, the study center should complete the relevant parts of the laboratory requisition and shipping forms, and explain the purpose of the kit to the patient.

If the Day 7 and Day 21 blood samples will not be drawn at the Investigator's study center, laboratory kits and shipping supplies will be provided at the following office visits:

- At the Day 1 office visit, the patient will be given the kit and shipping supplies for obtaining the Day 7 samples.
- At the Day 14 office visit, the patient will be given the kit and shipping supplies for obtaining the Day 21 samples.

4.5.7.2 Pregnancy test

There is no information on the use of nintedanib in pregnant women, but pre-clinical studies in animals have shown reproductive toxicity of this active substance. As nintedanib may cause foetal harm also in humans, it must not be used during pregnancy.

Female patients should be advised to notify their doctor or pharmacist if they become pregnant during therapy with nintedanib.

If the patient becomes pregnant while receiving nintedanib, she should be apprised of the potential hazard to the foetus. Termination of the treatment with nintedanib should be considered (Eu-SPC January 2016).

Based on findings from animal studies and its mechanism of action, nintedanib can cause fetal harm when administered to a pregnant woman. Nintedanib caused embryo-fetal deaths and structural abnormalities in rats and rabbits when administered during organogenesis at less than (rats) and approximately 5 times (rabbits) the maximum recommended human dose in adults. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to avoid becoming pregnant while receiving treatment with nintedanib and to use effective contraception during treatment and at least 3 months after the last dose of nintedanib ([Ofev® USPI 2014](#)USPI 2014).

There are no data from the use of pirfenidone in pregnant women.

In animals placental transfer of pirfenidone and/or its metabolites occurs with the potential for accumulation of pirfenidone and/or its metabolites in amniotic fluid.

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At high doses ($\geq 1,000$ mg/kg/day) rats exhibited prolongation of gestation and reduction in foetal viability (Esbriet® SmPC September 2015).

As a precautionary measure, it is preferable to avoid the use of pirfenidone during pregnancy.

For study patients of childbearing potential, serum pregnancy tests will be performed by the central laboratory at Screening, Day 1 (Baseline), the Week 24 or the Early Discontinuation Visit, and the final Follow-up Visit. In addition, a urine pregnancy test will be performed at the study center on Day 28, Day 56, Day 84, Day 112 and Day 140. If at any visit, a urine pregnancy test is positive, a serum pregnancy test must be drawn for confirmation.

For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of $< 1\%$ per year, during the treatment period and for at least 3 months after the final Follow-up Visit.

- A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a post-menopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
- Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Barrier methods must always be supplemented with the use of a spermicide.

For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

- With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $< 1\%$ per year during the treatment period and for at least 4 months after the final Follow-up Visit. Men must refrain from donating sperm during this same period.
- With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 4 months after the final Follow-up Visit.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.5.8 Electrocardiograms

All ECGs for this study will be 12-lead ECGs. They will be performed before bronchodilator administration or on a separate day. Use of short-acting bronchodilators will be prohibited in the 6 hours before the test, and use of long-acting bronchodilators will be prohibited in the 24 hours before the test. ECGs will be reviewed, initialled, and dated by the PI or designee within 24 hours of receipt.

Single ECG recordings will be obtained at specified timepoints, as outlined in the schedule of assessments (see [Appendix 1](#)), and may be obtained at unscheduled timepoints as indicated.

For safety monitoring purposes, the Investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at the site.

4.5.9 Patient-Reported Outcomes

The following PROs for this study will be analyzed in an exploratory manner:

[REDACTED]

4.5.10 Biomarker Study

[REDACTED]

4.6 PATIENT, TREATMENT, STUDY AND SITE DISCONTINUATION

4.6.1 Patient Discontinuation

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the Investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

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- Patient withdrawal of consent at any time
- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.6.2 Study Treatment Discontinuation

Patients who prematurely discontinue one or both study treatments will be withdrawn from the study.

Patients will be free to withdraw from the study at any time and without prejudice. Guidance for follow-up of patients who have been withdrawn from the study is provided in [Section 4.5.1.18](#).

Patients will be withdrawn from the study if any of the following occur:

- Interruption of pirfenidone, nintedanib, or both study treatments for ≥ 28 consecutive days
- An inability to tolerate nintedanib at a dose of 200 mg/d after initial up-titration (day 1-day 15)
- An elevation in liver test results of the magnitude described below
- A clinically significant vascular event, including bleeding or an arterial thromboembolic event
- GI perforation
- QTcF interval prolongation of the magnitude described below
- Any other TEAE or toxicity that is unacceptable in the opinion of the patient or Investigator
- Organ transplantation
- Use of a prohibited investigational therapy or concomitant medication
- Patient withdrawal of consent
- Pregnancy

Furthermore, patients can be withdrawn from the study for the following reasons:

- Non-adherence with the dosing regimen, including the dose-titration guidance for restarting study treatment
- At the Sponsor's or Investigator's discretion

A patient who is withdrawn from the study because of a photosensitivity reaction or rash will discontinue both pirfenidone and nintedanib treatment.

A patient who is withdrawn from the study for any other reason will discontinue nintedanib treatment. Whether pirfenidone treatment is discontinued will be left to the clinical judgment of the Investigator.

On completion of study participation, patients may be prescribed appropriate IPF treatment at the discretion of the treating physician.

Every attempt should be made to ensure that all patients who prematurely withdraw from the study return to the clinic as soon as possible (and ≤ 7 days after the decision to discontinue nintedanib) for an Early Discontinuation Visit. In addition, 28–35 days after the decision to discontinue nintedanib, such patients are to return to the clinic for a final Follow-up Visit.

If the patient has an AE that has not resolved at the time of study withdrawal, the clinic staff should obtain follow-up information.

4.6.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrolment is unsatisfactory.

The Sponsor will notify the Investigator if the Sponsor decides to discontinue the study.

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for Good Clinical Practice (GCP)
- No study activity (i.e. all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Pirfenidone and nintedanib are both approved and all relevant safety information is contained in their respective SmPCs / US-PIs. The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments as detailed below. For management of other adverse events, please consult the respective product labels (Esbriet® or Ofev®).

5.1.1 Management of Specific Adverse Events

This section describes the management of study treatment in the presence of the following TEAEs that are identified in the label of either pirfenidone or nintedanib:

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- elevated liver test results
- a photosensitivity reaction or rash
- nausea, vomiting, or diarrhea
- a clinically significant vascular event
- GI perforation.

5.1.1.1 Elevated Liver Test Results

Guidance for the management of study treatment in the presence of an elevated liver test result is provided in Table 4. Furthermore, the Investigator may contact the Medical Monitor or designee for consultation or to request clarification.

Table 4 Management of Dosing in Patients with Elevated Liver Test Results

Any elevation of either AAT or total bilirubin level:
Discontinue confounding medications, exclude other causes, and monitor the patient closely, including with repeat liver tests (weekly or more often), until the elevation resolves or stabilizes or until the end of the study, whichever comes first.
AAT 3 to 5 × ULN without hyperbilirubinemia:
Reduce or interrupt dosing with pirfenidone, nintedanib, or both study treatments, as clinically appropriate. Monitor the patient closely, including with repeat liver tests (weekly or more often), until the elevation resolves or stabilizes or until the end of the study, whichever comes first.
For a Dosing Interruption < 28 Consecutive Days:
After liver test results return to the normal range or Baseline values, restart study treatment if clinically appropriate, according to the guidance in Table 2.
If study treatment is restarted and the patient experiences another elevation in an AAT level of $\geq 3 \times \text{ULN}$ or any elevation in total bilirubin level $> \text{ULN}$, discontinue pirfenidone and nintedanib, and withdraw the patient from the study. Monitor the patient closely until the elevation resolves or stabilizes or until the end of the study, whichever comes first.
For a Dosing Interruption ≥ 28 Consecutive Days:
Discontinue pirfenidone and nintedanib, and withdraw the patient from the study. Monitor the patient closely until the elevation resolves or stabilizes or until the end of the study, whichever comes first.
AAT $\leq 5 \times \text{ULN}$ with symptoms or hyperbilirubinemia or AAT $> 5 \times \text{ULN}$ with or without hyperbilirubinemia:
Discontinue pirfenidone and nintedanib, and withdraw the patient from the study. Monitor the patient closely, including with repeat liver tests (weekly or more often), until the elevations resolves or stabilizes or until the end of the study, whichever comes first.

AAT = alanine or aspartate aminotransferase; ULN = upper limit of normal

5.1.1.2 Photosensitivity Reaction or Rash

If a patient develops a photosensitivity reaction or rash during combination treatment, the event should be managed as follows:

- Patients who experience a mild to moderate photosensitivity reaction or rash should be reminded of the instruction to use a sunblock daily and to avoid sun exposure. The dose of pirfenidone may be reduced to 3 capsules/day (1 capsule three times a day). If the rash persists after 7 days, pirfenidone should be discontinued for 15 days, with re-escalation to the recommended daily dose in the same manner as the dose escalation period.
- Patients who experience severe photosensitivity reaction or rash should be instructed to interrupt the dose and to seek medical advice. Once the rash has resolved, pirfenidone may be re-introduced and re-escalated up to the recommended daily dose at the discretion of the physician.
- Maintain the patient on the current dose of nintedanib, and do not increase the nintedanib dose if it is < 150 mg BID.
- Provide symptomatic treatment, and remind the patient about measures for sun avoidance
- If the photosensitivity reaction or rash resolves in < 28 consecutive days, decide whether it is clinically appropriate to restart pirfenidone treatment.
- If appropriate, restart pirfenidone as described in [Table 2](#).
- If pirfenidone treatment is not restarted, discontinue nintedanib and withdraw the patient from the study.
- If the photosensitivity reaction or rash persists for \geq 28 days, do not restart pirfenidone, discontinue nintedanib, and withdraw the patient from the study.

5.1.1.3 Nausea, Vomiting, or Diarrhea

If a patient who was on chronic treatment with pirfenidone, on a stable dose, for at least 16 weeks develops new nausea, vomiting, or diarrhea that persists despite appropriate supportive care and symptomatic treatment (e.g., adequate hydration, antiemetic medication, or antidiarrheal medication), the event(s) should be managed as follows:

- First, dose-reduce or interrupt nintedanib treatment; whether pirfenidone treatment is maintained, dose-reduced, or interrupted will be left to the judgment of the Investigator.
- Diarrhea should be treated at first signs with adequate hydration and anti-diarrheal medicinal products, e.g. loperamide, and may require treatment interruption. Nintedanib treatment may be resumed at a reduced dose (100 mg twice-daily) or at the full dose (150 mg twice-daily). In case of persisting severe diarrhea despite symptomatic treatment, therapy with nintedanib should be discontinued
- If patients experience significant adverse reactions, consider temporary dosage reductions or interruptions of pirfenidone to allow for resolution of symptoms
- In patients who experience intolerance to therapy due to gastrointestinal side effects, patients should be reminded to take the medicinal product with food. If symptoms persist pirfenidone may be reduced to 1-2 capsules (267 mg – 534 mg) 2-3 times/day with food with re-escalation to the recommended daily dose as tolerated. If symptoms continue, patients may be instructed to interrupt treatment for 1 to 2 weeks to allow symptoms to resolve.

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- If the nausea, vomiting, or diarrhea resolves or improves sufficiently in < 28 days, decide whether it is clinically appropriate to restart treatment. If appropriate, restart study treatment as described in [Table 2](#).
- If the nausea, vomiting, or diarrhea persists ≥ 28 days or is judged to be intolerable, discontinue nintedanib treatment (if not previously discontinued), and withdraw the patient from the study. Whether pirfenidone treatment is maintained, dose-reduced, or interrupted will be left to the judgment of the Investigator.

5.1.1.4 Clinically significant Vascular Event

If a patient has a clinical significant vascular event, including bleeding or an arterial thromboembolic event, discontinue nintedanib treatment, and withdraw the patient from the study. Whether pirfenidone treatment is maintained, dose-reduced, or interrupted will be left to the judgment of the Investigator.

5.1.1.5 Gastrointestinal Perforation

If a patient has a GI perforation, discontinue nintedanib treatment, and withdraw the patient from the study. Whether pirfenidone treatment is maintained, dose-reduced, or interrupted will be left to the judgment of the Investigator.

5.1.1.6 Management of Increases in QT Interval

Prolongation of the QTcF Interval

In the event of a QTcF interval > 550 ms or an increase from Baseline of > 60 ms, obtain a repeat ECG within 24 hours. If the QTcF finding is confirmed by the repeat ECG and verified by a study center or local cardiologist, discontinue pirfenidone and nintedanib treatment, and withdraw the patient from the study.

In the event of a QTcF interval of 500–550 ms or an increase from Baseline of 31–60 ms, obtain a repeat ECG within 24 hours. If the QTcF finding is confirmed by the repeat ECG and verified by a study center or local cardiologist, interrupt pirfenidone and nintedanib treatment. If an alternative explanation is identified (e.g. electrolyte abnormality or concomitant medication) and the abnormality resolves, restarting study treatment can be considered by the Investigator in consultation with the Medical Monitor or designee. If the Investigator, in consultation with the Medical Monitor or designee, considers it clinically appropriate to restart study treatment, restart treatment as described in [Table 2](#).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording AEs, including SAEs and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in [Section 5.4](#).

5.2.1 Adverse Events

According to the ICH guideline for GCP, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in [Section 5.3.5.8](#)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death)
- This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see [Section 5.3.5.9](#))
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see [Section 5.3.3](#)); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see [Section 5.4.2](#) for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see [Section 5.4.2](#) for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see [Section 5.3.5.6](#))
- Suspected transmission of an infectious agent by the study drug, as defined below:
Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all adverse events (see [Section 5.2.1](#) for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in [Section 5.4](#) to [Section 5.6](#). For each adverse event recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (see [Section 5.2.2](#) for seriousness criteria), severity (see [Section 5.3.3](#)) and causality (see [Section 5.3.4](#)).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of combination treatment on Day 1**, only SAEs caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see [Section 5.4.2](#) for instructions for reporting SAEs).

After initiation of combination treatment on Day 1, all adverse events will be reported until 28 days after the last dose of study drug. After this period, the Investigator should report any SAEs that are believed to be related to prior study drug treatment (see [Section 5.6](#)).

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (version 4.03) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE version 4.03 which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

- Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
- If an event is assessed as a "significant medical event," it must be reported as a SAE (see [Section 5.4.2](#) for reporting instructions), per the definition of SAE in [Section 5.2.2](#).
- Grade 4 and 5 events must be reported as SAEs (see [Section 5.4.2](#) for reporting instructions), per the definition of SAE in [Section 5.2.2](#).

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration

- Temporal relationship of event onset to the initiation of study drug

- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe GI hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.

- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see [Section 5.4.2](#) for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see [Section 5.3.5.3](#) for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the Investigator's judgment

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high BP), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see [Section 5.3.5.3](#) for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ baseline value) in combination with either an elevated total bilirubin ($>2\times$ ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with total bilirubin $>2\times$ ULN (of which $\geq 35\%$ is direct bilirubin)
- Treatment-emergent ALT or AST $>3\times$ baseline value in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see [Section 5.2.3](#)).

Guidance for the management of study treatment in the presence of an elevated liver test result is provided in [Table 4](#). Furthermore, the Investigator may contact the Medical Monitor or designee for consultation or to request clarification.

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see [Section 5.3.1](#)), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see [Section 5.4.2](#)). This includes death attributed to progression of IPF.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "**sudden death**" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "**unexplained death**" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

If the death is attributed to progression of IPF "IPF progression" should be recorded on the Adverse Event eCRF.

5.3.5.8 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A pre-existing medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.9 Lack of Efficacy or Worsening of IPF

Medical occurrences or symptoms of deterioration that are anticipated as part of IPF should be recorded as an adverse event if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of IPF on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated Idiopathic Pulmonary Fibrosis").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., in-patient admission to a hospital) or prolonged hospitalization should be documented and reported as a SAE (per the definition of SAE in [Section 5.2.2](#)), except as outlined below.

The following hospitalization scenarios are not considered to be adverse events:

- Hospitalization for respite care

- Hospitalization for a pre-existing condition, provided that all of the following criteria are met:
 - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

The following hospitalization scenarios are not considered to be SAEs, but should be reported as adverse events instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available
- The patient has not experienced an adverse event.

5.3.5.11 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see [Section 5.4.2](#)).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the Investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs (see [Section 5.4.2](#) for further details)
- Adverse events of special interest (see [Section 5.4.2](#) for further details)
- Pregnancies (see [Section 5.4.3](#) for further details)

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the Investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all Investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Initiation of Combination Treatment

After informed consent has been obtained but prior to initiation of combination treatment on Day 1, only SAEs caused by a protocol-mandated intervention should be reported. The SAE/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to Investigators.

5.4.2.2 Events That Occur after Initiation of Combination Treatment

After initiation of combination treatment, SAEs and non-serious adverse events of special interest will be reported until 28 days after the last dose of study drug. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the SAE/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to Investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting post-study adverse events are provided in [Section 5.6](#).

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 3 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. The Investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, the Clinical Trial Pregnancy Reporting Form provided to Investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to Investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Pregnancies in Female Partners of Male Patients /Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 4 months after the last dose of study drug. A Pregnancy Report eCRF should be completed by the Investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the Investigator will update the Pregnancy Report eCRF with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 4 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to Investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health

Information to allow for follow-up on her pregnancy. After the authorization has been signed, the Investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An Investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

Any abortion should be classified as a SAE (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see [Section 5.4.2](#)).

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug (or the female partner of a male patient exposed to study drug) should be classified as a SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see [Section 5.4.2](#)).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in [Section 5.4.3.1](#).

5.5.2 Sponsor Follow-Up

For SAEs, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Sponsor should be notified if the Investigator becomes aware of any SAE that occurs after the end of the adverse event reporting period (defined as 28 days after the

last dose of study drug), if the event is believed to be related to prior study drug treatment.

These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all SAEs and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, ECs and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference documents:

- Local prescribing information SmPC / US-PI for Esbriet® and Ofev®

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

This is a safety and tolerability study; it is not designed to assess the efficacy of combination treatment. Thus, no formal statistical hypotheses will be assessed, and the analysis will be limited to descriptive statistics. Percentages will be calculated based on the number of patients with non-missing data, unless otherwise indicated.

6.1 ANALYSIS POPULATION

One analysis population has been defined: The Safety Population will consist of all patients who received at least one dose of nintedanib or pirfenidone at the Baseline Visit (Day 1).

The primary (safety) endpoint is:

- Proportion of patients who complete 24 weeks of combination treatment on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d

The secondary (safety) endpoints are:

- Proportion of patients who discontinue pirfenidone, nintedanib, or both study treatments because of adverse events before the Week 24 Visit

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- Total number of patient days of combination treatment with pirfenidone and nintedanib
- Total number of days from the initiation of combination treatment to discontinuation of pirfenidone, nintedanib, or both study treatments

6.2 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 80 patients was selected based on the AE discontinuation rates after one year observed in the randomized Phase 3 pirfenidone studies and the randomized Phase 2 and 3 nintedanib studies (pirfenidone 14.6% AE discontinuation [Esbriet® USPI 2014]; nintedanib 21% AE discontinuation [Ofev® USPI 2014]). Given that for pirfenidone the discontinuation rate after 24 weeks was 6%-8% in studies PIPF-004 and PIPF-006 it is a reasonable assumption that the nintedanib discontinuation rate was around 10%-11%. As in this study of combination treatment, it is possible that the addition of nintedanib to ongoing pirfenidone treatment could increase the proportion of patients who discontinue because of an AE, given the overlap in the GI and hepatic effects of pirfenidone and nintedanib.

Assuming 85% of the patients complete 24 weeks of combination treatment, a sample size of 80 patients would be expected to yield an actual completion rate of 77.2% - 92.8% using a 95% confidence interval (CI). Table 6 shows the 95% CIs associated with projected completion rates of 75%, 80%, 85%, 90% or 95%, assuming an 80-patient sample size.

Table 6 Confidence Intervals Associated with Projected Completion Rates of 75% to 95%, and a Sample Size of 80 Patients

Number of Patients who completed 24 weeks	Proportion of Patients who completed 24 weeks	Lower Bound of 95% CI	Upper Bound of 95% CI
76	95.0%	90.2%	99.8%
72	90.0%	84.4%	96.6%
68	85.0%	77.2%	92.8%
64	80.0%	71.2%	88.8%
60	75.0%	65.5%	84.5%

CI = confidence interval

Patients who are withdrawn from the study will not be replaced.

6.3 SUMMARIES OF CONDUCT OF STUDY

Patient enrollment, study treatment administration, and reasons for treatment discontinuation and study discontinuation will be summarized for all enrolled patients. In addition, protocol deviations and eligibility violations will be summarized by frequency tables.

6.4 SUMMARIES OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

There is only one treatment group in this study. There are no formal statistical hypothesis tests to be performed and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

Baseline and disease characteristics such as demographics, medical history, etc. will be summarized by descriptive statistics (frequency tables for categorical variables and mean, median, range, standard deviation, and 25th - 75th quartiles for the continuous variables). These characteristics will be summarized for the safety population, which is defined as the population that includes all patients enrolled in the study who received at least one dose of nintedanib or pirfenidone at the Baseline visit (Day 1).

6.5 EFFICACY ANALYSES

The efficacy measures of this study will only be analyzed in an exploratory manner and are as follows:

[REDACTED]

Patient-Reported Outcome Measures:

The PRO objectives for this study are as follows:

[REDACTED]

6.6 SAFETY ANALYSES

Safety Measures are as follows:

- Number of patients who completed 24 weeks of combination therapy
- Frequency of TEAEs and Treatment-Emergent Serious Adverse Events (TESAEs)
- Gastrointestinal side effects
- Hepatic side effects
- Physical examination findings, including vital signs measurements, body weight (kg), and body mass index (BMI)
- Clinical laboratory tests
- ECGs

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- Early study treatment discontinuation, including reasons
- Deaths and cause of deaths

AEs will be coded to a preferred term and system organ class using the Medical Dictionary for Regulatory Activities (MedDRA). An AE occurring on the day of the initiation of combination treatment (Day 1) through 28 days after the last dose of combination treatment will be considered treatment emergent. Laboratory abnormalities will be graded using the CTCAE (CTEP 2010), version 4.03. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

The extent of exposure will be summarized.

Data summaries will be provided for the following:

- the number and proportion of patients who complete 24 weeks of combination treatment on pirfenidone at a dose of 1602–2403 mg/d and nintedanib at a dose of 200–300 mg/d (with 95% CI)
- the numbers and proportions of patients with a dose reduction or a dose interruption
- the number and proportion of patients who discontinued combination treatment because of a AE (with 95% CI)
- the total number of days on combination treatment at an pirfenidone dose of 1602–2403 mg/d and an nintedanib dose of 200–300 mg/d
- the total number of days from the start of combination treatment to discontinuation of one or both study treatments
- the final prescribed doses of pirfenidone and nintedanib at the end of combination treatment
- reasons for premature discontinuation of combination treatment.

In addition, logistic regression analysis will be used for the discontinuation rate to assess the influence of baseline covariates in an exploratory manner. Details of those analyses will be provided in the Statistical Analysis plan.

AEs and SAEs leading to treatment discontinuation will be summarized by preferred term and system organ class, and severity, seriousness, and relationship to treatment as recorded by the Investigator.

Additional summaries will be provided for:

- the numbers and proportions of patients with a Major Adverse Cardiac Event (MACE), a cerebrovascular event, a bleeding event, or a thromboembolic event
- the numbers and proportions of patients discontinuing combination treatment for a liver test abnormality, a GI event, or photosensitivity reaction/rash
- the numbers and proportions of patients with an emergency department visit or hospitalization
- deaths.

Observed and change values for vital signs and clinical laboratory data will be summarized descriptively. Grade 3 and 4 laboratory abnormalities will be summarized by

CTCAE grade, and shift tables by CTCAE grade will be provided. If no CTCAE grade is available for a specific laboratory variable, the shift table will summarize the data by the normal range. ECG data will be summarized, presenting the numbers and proportions of patients with a maximum QTcF interval < 500 ms, 500–550 ms, and > 550 ms; with a maximum change from the baseline QTcF interval of ≤ 30 ms, 31–60 ms, and > 60 ms; and with ECG changes considered by the Investigator to be clinically significant.

Prior and concomitant medications will be summarized by class.

6.7 INTERIM ANALYSIS

Throughout the study, an external independent Data Monitoring Board (iDMC) will review individual SAE reports and laboratory toxicities. In addition, the iDMC is scheduled to review safety data and advise on study conduct at least three times during the study: when the first approximately 20 patients have completed 8 weeks of combination treatment or permanently discontinued study treatment, when approximately 50% of the total patient group has completed 12 weeks of combination treatment or permanently discontinued study treatment, and when approximately 75% of the total patient group has completed 24 weeks of combination treatment or permanently discontinued study treatments. The iDMC may recommend that the Sponsor stop the study for safety concerns set forth in the iDMC Charter. Enrollment will continue during iDMC review of the 8-week data, unless the iDMC recommends that enrollment be paused or halted. Additional ad hoc meetings or data review can be requested by the iDMC or Sponsor, if warranted. Additional information is provided in the iDMC Charter.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion.

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eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the Investigator or a designee.

At the end of the study, the Investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in [Section 7.5](#).

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e. in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (E.U.) or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The Investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see [Section 9.6](#)).

In addition to the requirements for reporting all adverse events to the Sponsor, Investigators must comply with requirements for reporting SAEs to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the Investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The Investigator should document and explain any protocol deviations. The Investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The Investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The study will be overseen by study management team of the Sponsor consisting of clinical study manager, experienced medical staff (International Medical Director), statistician and a data management team

Study monitoring, including data collection (source verification), site initiation and visits and adverse processing (Medical Monitor) will be conducted by a Clinical Research Organization (CRO). The management of the database will also be done by the CRO with final data and database transferred to Roche. The safety of the study will be monitored by an iDMC consisting of 2 clinicians and one statistician experienced in conduct and safety review of controlled clinical studies. The iDMC will review interim analysis for safety and, if needed further safety data and give recommendation to the Sponsor. The study will be conducted using IxRS and central lab provider.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

<http://www.rochetrials.com/pdf/RocheGlobalDataSharingPolicy.pdf>

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The Investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1 Schedule of Assessments

	Study Period																Follow-up	Early d/c
	W/O [a]	Screening [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Informed consent [d]	X	X																
Complete medical history [e]	X	X																
Directed medical history [f]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pirfenidone treatment history	X	X [g]	X [h]															
Document IPF diagnosis		X																
Complete physical examination, including vital signs [i]		X	X		X		X		X		X		X		X	X	X	X

Appendix 1 (cont.)

	Study Period																Follow-up	Early d/c
	W/O [a]	Screening [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d										Refer to foot note for timing [b]
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140	168		
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20	24		
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Body weight (kg)		X	X		X		X		X		X		X		X	X	X	X
Height (cm)		X																
12-lead ECG [j]		X	X													X	X	X
Spirometry (FVC), and DLco [k]		X	X								X					X		X
Spirometry (FEV1) [k]		X	X															
Hematology, serum chemistry [l], CRP		X	X [m]	X [m]	X [m]	X [m]	X		X		X		X		X	X	X	X
Urine pregnancy test [n]							X [r]		X [r]		X [r]		X [r]		X [r]	X [r]		
Serum pregnancy test [n]		X	X													X	X	X
Biomarker sample collection [o]			X				X									X		X

Appendix 1 (cont.)

	Study Period																Follow-up	Early d/c
	W/O [a]	Screening [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Review patient diary			X		X		X		X		X		X		X	X	X	X
Review AEs [p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review pirfenidone dosing adherence [p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Review nintedanib dosing adherence [p]				X	X	X	X	X	X	X	X	X	X	X	X	X		X
Review concomitant medications [p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review inclusion / exclusion criteria	X	X	X															
Obtain historical FEV1, FVC and DLco data [q]		X																

Appendix 1 (cont.)

	Study Period																Follow-up	Early d/c
	W/O [a]	Screening [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d										Refer to foot note for timing [b]
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140	168		
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20	24		
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Perform [REDACTED]			X													X		X
Dispense/collect patient diary		X															X	
Dispense wallet card			X															
Dispense pirfenidone and explain dosing		X	X						X				X					
Dispense nintedanib and explain dosing			X						X				X					
Instruct to resume commercial pirfenidone and explain dosing																X		X
Collect unused pirfenidone and empty bottles			X						X				X			X		X

Appendix 1 (cont.)


	Study Period																Follow-up	Early d/c
	W/O [a]	Screen- ing [a]	Combination Treatment															
				Visit Window, ± 3 d				Visit Window, ± 7 d								Refer to foot note for timing [b]	ASAP ≤ 7 d after decision to d/c nintedanib [c]	
Study Day:	-50 to -22	-21 to -1	1 (BL)	7	14	21	28	42	56	70	84	98	112	126	140			168
Study Week:				1	2	3	4	6	8	10	12	14	16	18	20			24
Type of Contact:	O	O	O	P	O	P	O	P	O	P	O	P	O	P	O	O	O	O
Assessment																		
Collect unused nintedanib and empty bottles									X				X			X		X

AE = adverse event; ASAP = as soon as possible; BL = Baseline; d = day; d/c = discontinue; DLco = carbon monoxide diffusing capacity; ECG = electrocardiogram; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; [REDACTED] O = office visit; P = telephone contact; SAE = serious adverse event; W/O = Washout

- Patients taking prohibited medications enter Washout; if prohibited medication must be tapered, patient must be off that medication 28 days before start of Screening. Other patients directly enter Screening.
- For patients who complete 24 weeks of study treatment, visit should occur 28–35 days after completion of combination treatment. For patients who prematurely discontinue study treatment or have a treatment interruption of ≥ 28 consecutive days, visit should occur 28–35 days after decision to discontinue nintedanib.
- If a patient cannot return in ≤ 7 days, study center is to call patient to review medical history and to send laboratory kit and shipping supplies to patient so that blood samples can be drawn at another study center, commercial laboratory or by home nursing agency; Early Discontinuation Visit should then be scheduled as soon as possible.
- Written informed consent must be obtained before any study-mandated assessment or procedure, including tapering and/or discontinuing prohibited medication. If written informed consent was not obtained at Washout, it must be obtained at start of Screening.
- Including systems review, and review of concomitant medications, events in 28 days before start of Screening, and historical data (including prior high-resolution computed tomography scans, pulmonary function tests, and surgical lung biopsy data, if available). If complete medical history was obtained

Appendix 1 (cont.)

during Washout, during Screening the list of concomitant medications and medical history should be updated with changes since patient signed informed consent form.

- f. Includes AEs, concomitant medications, dosing adherence, hospitalizations, inquiry regarding compliance with protocol requirements for contraceptive use and avoiding tobacco products, and inquiry regarding whether patient is aware of being pregnant.
- g. At start of Screening, patient must have been on pirfenidone for ≥ 16 weeks and on stable dose (1602–2403 mg/d) for ≥ 28 days; dose must be expected to remain in that range throughout study. Treatment interruptions > 7 days are not permitted in the 28 days before start of Screening.
- h. At Baseline Visit, patient must have been at least approximately 80% adherent to pirfenidone dosing regimen since Screening Visit.
- i. Resting BP and HR, respiratory rate, body temperature.
- j. To be performed before laboratory assessments; use of short-acting bronchodilators is prohibited in preceding 6 hours, and use of long-acting bronchodilators is prohibited in preceding 24 hours.
- k. Spirometry (FVC, FEV1) is done before and approximately 30 minutes after short-acting bronchodilator administration; DLco testing is done before or at least 30 minutes after last puff of short-acting bronchodilator. Use of short-acting bronchodilators is prohibited in 6 hours before start of pre-bronchodilator spirometry test or a pre-bronchodilator DLco test. Use of long-acting bronchodilators is prohibited in 24 hours before start of tests.
- l. Including creatinine clearance rate, calculated using Cockcroft-Gault formula.
- m. If sample cannot be drawn at investigator's study center on Days 7 and Day 21, it can be drawn at another study center, commercial laboratory or by a home nursing agency. Patient is to be given laboratory kit and shipping supplies at Day 1 Visit (for Day 7 blood draw) and Day 14 Visit (for Day 21 blood draw).
- n. Women of childbearing potential.
- o. 
- p. Done as part of patient diary review at office visits from Week 2 through Week 24 or Early Discontinuation Visit (for dosing adherence) or through final Follow-up Visit (for AEs and concomitant medications).
- q. If available, obtain percent predicted FVC, FEV1 and percent predicted DLco measurements from 12 months before start of Screening (from documented pulmonary function laboratory reports)
- r. If urine pregnancy test is positive, a serum pregnancy test must be drawn for confirmation.