

Observational and Non-Interventional Study (ONIS) New Data Collection Protocol

Document Number:	c45099814-01
Boehringer Ingelheim (BI) Study Number:	1199-0545
BI Investigational Product(s):	Nintedanib
Title:	Observational, multicentre, prospective, real-world post-authorization safety study describing the achievement of nintedanib-associated DI arrhoea control after 12 weeks of follow-up in patients with idiopathic pu L monary FIB rosis (IPF) and progressive pulmonary fibrosis (other than IPF) in Spain: the DIALFIB study
Brief lay title:	A study based on medical records in Spain that looks at diarrhoea control in people with pulmonary fibrosis who are taking nintedanib
Protocol version identifier:	V 3.0
Date of previous version of protocol:	29 Dec 2023
Post-Authorisation Safety Study (PASS):	Yes
EU Post-Authorisation Studies (PAS) register number:	EUPAS106524
Active substance:	Active substance: Nintedanib Anatomical therapeutic chemical (ATC) code: L01EX09
Medicinal product:	Nintedanib
Product reference:	EU/1/14/979
Procedure number:	Not applicable
Marketing authorisation holder(s) (MAH):	<u>MAH:</u> Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein, Germany <u>This study is initiated, managed, and sponsored by:</u>

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ONIS New Data Collection Protocol

Study number: 1199-0545

Document number: c45099814-01

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	Boehringer Ingelheim España, S.A. C/ Prat de la Riba, 50 08174 Sant Cugat del Vallés (Barcelona)
Joint PASS:	No
Research question and objectives:	<p><u>Main research question(s):</u></p> <p>Among patients with IPF and progressive pulmonary fibrosis (PPF) (other than IPF) treated with 150 mg bid of nintedanib suffering a first episode of nintedanib-associated diarrhoea in real-world settings in Spain, which is the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up?</p> <p>Primary Objective:</p> <p>To describe the proportion of patients who achieve diarrhoea control while taking a nintedanib dose of 150 mg bid at 12-week follow-up in patients with IPF and other PPF reporting a first episode of nintedanib-associated diarrhoea.</p> <p>Secondary Objectives:</p> <ol style="list-style-type: none">To describe the change in the proportion of patients taking the optimal nintedanib dose (150 mg bid) at 12-week follow-up referent to diarrhoea initiation.To describe changes in diarrhoea indicators (Bristol Stool Form Scale [BSFS] and number of stools per day) and changes in body weight at 12-week follow-up referent to diarrhoea initiation.To describe the proportion of patients using carob flour for the management of nintedanib-associated diarrhoea at any time from diarrhoea initiation to 12-week follow-up.To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at diarrhoea initiation and at 12-week follow-up.To describe the nintedanib utilization pattern (occurrence of dose reductions from 150 mg bid to 100 mg bid, permanent withdrawal, and escalations from 100 mg bid to 150 mg bid) in the study population from diarrhoea initiation to 12-week follow-up. <p>Further objectives:</p> <ol style="list-style-type: none">To describe changes in diarrhoea indicators (BSFS and number of stools per day) and changes in body weight at 6-week follow-up referent to diarrhoea initiation.To describe the number of patients who do not receive treatment for nintedanib-associated diarrhoea in all the study period (i.e., from diarrhoea initiation to 12-week follow-up).To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at 6-week follow-up referent to diarrhoea initiation.

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	<div>4. To describe the counts of different treatment combinations (e.g., loperamide + carob flour) used at least once for the management of nintedanib-associated diarrhoea from diarrhoea initiation to 12-week follow-up.</div> <div>5. To describe the occurrence of at least one episode of persistent diarrhoea (lasting ≥14 days) and the number of persistent diarrhoea episodes in the study population from diarrhoea initiation to 12-week follow-up.</div> <div>6. To describe the duration of the first nintedanib-associated diarrhoea episode.</div> <div>7. To describe the time from nintedanib initiation to the first nintedanib-associated diarrhoea episode.</div> <div>8. To describe the occurrence of at least one nintedanib temporary interruption from diarrhoea initiation to 12-week follow-up.</div>
Country(-ies) of study:	Spain
Author:	<div>Lead Epidemiologist: [REDACTED]</div> <div>[REDACTED]</div> <div>Engagement Manager: [REDACTED]</div> <div>[REDACTED]</div> <div>Statistician: [REDACTED]</div>
MAHs:	Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein, Germany
MAH contact person:	RWE Manager, [REDACTED], Boehringer Ingelheim [REDACTED]
EU-QPPV:	[REDACTED], Boehringer Ingelheim [REDACTED]
Signature of EU-QPPV:	The signature of the EU-QPPV is provided electronically
Date:	29 Oct 2024
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ADL	Activities of Daily Living
ATC	Anatomical Therapeutic Chemical
BI	Boehringer Ingelheim
Bid	Twice per day
BSFS	Bristol Stool Form Scale
CA	Competent Authority
CDA	Confidentiality Agreement
CRA	Clinical Research Associate
CRO	Clinical research organization
CTCAE	Common Terminology Criteria for Adverse Events
DMRP	Data Management and Review Plan
EC	Ethics Committee
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group scale
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMR	Electronic Medical Records
EU	European Union
FDA	Food and Drug Administration
FVC	Forced Vital Capacity
GI	Gastrointestinal
GPP	Good Pharmacoepidemiology Practices
HTTPS	Hypertext Transfer Protocol Secure
ICD	International Statistical Classification of Diseases and Related Health Problems
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
ILDs	Interstitial Lung Diseases
iPD	Important Protocol Deviation
IPF	Idiopathic Pulmonary Fibrosis
ISF	Investigator Site File
MAH	Marketing Authorisation Holder
MSL	Medical Scientific Liaison
ONIS	Observational and Non-Interventional Study
OPU	Operative Project Unit
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PD	Protocol Deviation
PF-ILD	Progressive Fibrosing Interstitial Lung Diseases
PIS	Patient Information Sheet
PPF	Progressive Pulmonary Fibrosis
PS	Performance Status
PSP	Patient Support Programme
SAE	Serious Adverse Event
SEAP	Statistical and Epidemiological Analysis Plan
SFQ	Site Feasibility Questionnaire

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SIV	Site Initiation Visit
SSc	Systemic Sclerosis
SSc-ILD	Systemic Sclerosis associated Interstitial Lung Diseases
SSL	Secure Sockets Layer
SOP	Standard Operating Procedure
TKI	Tyrosine Kinase Inhibitor

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3. RESPONSIBLE PARTIES

Boehringer Ingelheim:

Study role	Contact
ONIS Lead Manager	
ONIS Lead	
Real World Data and Scientific Analytics Manager	
ONIS Lead Associate	
Medical Advisor Team	
Market Access & Healthcare Affairs Team	
Coordinating investigator	

Study role	Contact
Principal in charge	
Contract Research Organization (CRO) Project Manager	
Lead Epidemiologist	
ONIS Statistician	
ONIS Data Manager	

The list of all participating sites and investigators is available as a stand-alone document (see [Annex 1](#)).

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4. ABSTRACT

Name of company: Boehringer Ingelheim.			
Name of finished medicinal product: Nintedanib.			
Name of active ingredient: Active substance: Nintedanib. Anatomical therapeutic chemical (ATC) code: L01EX09			
Protocol date: 06 Nov 2023	Study number: 1199-0545	Version/Revision: V3.0	Version/Revision date: 29 Oct 2024
Title of study:	Title: Observational, multicentre, prospective, real-world post-authorization safety study describing the achievement of nintedanib-associated DI Arrhoea control after 12 weeks of follow-up in patients with idiopathic puLmonary FIB rosis (IPF) and progressive pulmonary fibrosis (other than IPF) in Spain: the DIALFIB study Brief lay title: A study based on medical records in Spain that looks at diarrhoea control in people with pulmonary fibrosis who are taking nintedanib		
Rationale and background:	<p>In the last decade, the treatment of patients with IPF and other progressive pulmonary fibrosis (PPFs) have made substantial improvements, based on novel therapies. Nintedanib, one of the two treatments available for IPF and the only treatment available for other PPFs, is a tyrosine kinase inhibitor (TKI) that acts by blocking tyrosine kinase enzymes of lung cells receptors, inhibiting the generation of fibrotic tissue (1, 2). Despite its proven benefits, nintedanib is not exempt of adverse events (AE), with the most frequent being diarrhoea (1-5). Indeed, 66.9% to 75.7% of nintedanib-treated patients (2-5), present diarrhoea. Although most (95%) of nintedanib AEs are categorized as not serious (6), the high prevalence of diarrhoea and its potential impact on patients health status, often leads to dosage reduction or -in around 13%- to treatment discontinuation (5, 7-9). In this context and considering the limited treatment alternatives for IPF and other PPFs, it is essential to describe the real-world proportion and characteristics of patients who achieve control of nintedanib-associated diarrhoea.</p> <p>This study aims to describe the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up among patients with IPF and other PPF having a first episode of nintedanib-associated diarrhoea in real world settings in Spain. It is expected that the study findings would suggest potential alternatives to address this problem and guide future studies aiming to prove the effectiveness of anti-diarrhoea treatments in this population.</p>		

Research question and objectives:	<p><u>Main research question:</u></p> <p>Among patients with IPF and progressive pulmonary fibrosis (PPF) (other than IPF) treated with 150 mg bid of nintedanib suffering a first episode of nintedanib-associated diarrhoea in real-world settings in Spain, which is the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up?</p> <p>Primary Objective:</p> <ol style="list-style-type: none">1. To describe the proportion of patients who achieve diarrhoea control while taking a nintedanib dose of 150 mg bid at 12-week follow-up in patients with IPF and other PPF reporting a first episode of nintedanib-associated diarrhoea. <p>Secondary Objectives:</p> <ol style="list-style-type: none">1. To describe the change in the proportion of patients taking the optimal nintedanib dose (150 mg bid) at 12-week follow-up referent to diarrhoea initiation.2. To describe changes in diarrhoea indicators (Bristol Stool Form Scale [BSFS] and number of stools per day) and changes in body weight at 12-week follow-up referent to diarrhoea initiation.3. To describe the proportion of patients using carob flour for the management of nintedanib-associated diarrhoea at any time from diarrhoea initiation to 12-week follow-up.4. To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at diarrhoea initiation and at 12-week follow-up.5. To describe the nintedanib utilization pattern (occurrence of dose reductions from 150 mg bid to 100 mg bid, permanent withdrawal, and escalations from 100 mg bid to 150 mg bid) in the study population from diarrhoea initiation to 12-week follow-up. <p>Further objectives:</p> <ol style="list-style-type: none">1. To describe changes in diarrhoea indicators (BSFS and number of stools per day) and changes in body weight at 6-week follow-up referent to diarrhoea initiation.2. To describe the number of patients who do not receive treatment for nintedanib-associated diarrhoea in all the study period (i.e., from diarrhoea initiation to 12-week follow-up).3. To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at 6-week follow-up referent to diarrhoea initiation.4. To describe the counts of different treatment combinations (e.g., loperamide + carob flour) used at least once for the management of nintedanib-associated diarrhoea from diarrhoea initiation to 12-week follow-up.
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	<ol style="list-style-type: none"> 5. To describe the occurrence of at least one episode of persistent diarrhoea (lasting ≥ 14 days) and the number of persistent diarrhoea episodes in the study population from diarrhoea initiation to 12-week follow-up. 6. To describe the duration of the first nintedanib-associated diarrhoea episode. 7. To describe the time from nintedanib initiation to the first nintedanib-associated diarrhoea episode. 8. To describe the occurrence of at least one nintedanib temporary interruption from diarrhoea initiation to 12-week follow-up.
Study design:	<p>This is an observational, non-interventional, multicentre, and prospective, real-world post authorization safety study (PASS), that will describe the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up in patients with IPF and other PPF who report a first nintedanib-related diarrhoea episode in hospital settings in Spain. It will be conducted using primary data collected during routine medical consultations, which will be complemented with secondary data extracted from electronic medical records (EMR) and recorded by pulmonologists (or delegates) in an electronic case report form (eCRF). Index date will be defined as the date of diarrhoea initiation and study baseline will be defined as the first face-to-face patient visit with their pulmonologist due to a first episode of diarrhoea after the initiation of nintedanib. Baseline visit will be performed as close as possible to index date and maximum 4 weeks after index date). Patients will be assessed at study baseline and at 3-, 6-, and 12-week follow-up after study baseline.</p>
Population:	<p>This study will include all patients diagnosed with IPF and other PPF who report a first episode of diarrhoea while being treated with nintedanib optimal dose (150 mg twice per day [bid]). The study duration will be from the start of the recruitment period (which will last approximately 6 months) to the last follow-up visit of the last patient (approximately 9 months of total study period) and will be conducted in hospital settings in Spain. Patients will be followed-up from baseline until death, loss of follow-up, or end of study follow-up (12 weeks), whichever comes first. Eligible patients will be competitively recruited according to the following inclusion and exclusion criteria:</p> <p>Inclusion criteria</p> <ol style="list-style-type: none"> 1. Adults (≥ 18 years old) at diarrhoea initiation. 2. Ability to consent and to conduct all procedures of the study, as judged by the study investigator, and agreeing to participate providing informed consent at baseline. 3. Diagnosis of IPF or PPF (other than IPF), as registered in EMR using free text or using disease codes (International Statistical Classification of Diseases and/or Related Health Problems 9th and 10th Revision (ICD-9 and/or ICD-10), at least 1 day before diarrhoea initiation. 4. Being treated with 150 mg bid of nintedanib when initiating diarrhoea symptoms, defined as having a registered nintedanib ATC code (L01EX09) or the molecule/commercial name registered in the EMR, for at least 1 day before diarrhoea initiation.

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	<div>5. First face to face pulmonologist consultation at the time of recruitment due to a first diarrhoea episode since nintedanib initiation. Diarrhoea defined as the passage of three or more loose or liquid stools in a 24- hour period (loose or liquid stools defined as stools with BSFS of 6 or 7 points).</div> <div>Exclusion criteria</div> <div><div>1. Patients diagnosed with systemic sclerosis associated interstitial lung disease (SSc-ILD) as registered in EMR using free text or ICD codes (ICD-9 and/or ICD-10). Referent to any time before or at diarrhoea initiation.</div><div>2. Participation in any clinical trial including a drug or device. Referent to any time before or at diarrhoea initiation.</div><div>3. Participation in any Patient Support Programme (PSP) at diarrhoea initiation.</div><div>4. Having history of chronic gastrointestinal disorder (e.g., inflammatory bowel disease or the short gut syndrome), pancreatic dysfunction/insufficiency, or colon cancer; due to the likelihood of faecal incontinence. Referent to any time before or at diarrhoea initiation.</div><div>5. Having a performance status (PS) ≥3 points on the Eastern Cooperative Oncology Group (ECOG) scale at diarrhoea initiation, due to the likelihood of faecal incontinence.</div></div>
Variables:	<div>Demographic/clinical characteristics</div> <div><div>• Age, years</div><div>• Sex</div><div>• Race/ ethnicity</div><div>• Body mass index (or weight and height), kg/m²</div><div>• Smoking status</div><div>• Pulmonary disease: IPF/PPF (type of PPF) and date of diagnosis</div><div>• Comorbidities and date of diagnosis<ul style="list-style-type: none">○ Arterial hypertension○ Diabetes○ Gastroesophageal reflux○ Coronary heart disease○ Sleep apnoea-hypopnea syndrome○ Heart disease○ Asthma○ Chronic bronchitis○ Chronic Obstructive Pulmonary Disease○ Emphysema○ Lung cancer○ Other relevant comorbidities: names and dates</div></div> <div>Health indicators</div> <div><div>• Forced Vital Capacity (FVC), in litres</div><div>• Diffusing Capacity of Lung for Carbon Monoxide, (% predicted)</div><div>• ECOG scale, score</div></div>

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	<p>Diarrhoea control achievement, yes/no (<3 loose or liquid stools in a 24-hour period, while being treated with 150 mg bid of nintedanib)</p> <p>Diarrhoea indicators and body weight</p> <ul style="list-style-type: none">• Number of stools per day• BSFS score• Body weight, kilograms <p>Persistent diarrhoea episode</p> <ul style="list-style-type: none">• Occurrence of persistent diarrhoea episode yes/no• Number of persistent diarrhoea episodes <p>Duration of first nintedanib-associated diarrhoea episode, days</p> <p>Time from nintedanib initiation to the first diarrhoea episode, days</p> <p>Nintedanib use</p> <ul style="list-style-type: none">• Optimal dose• Dose reduction• Drug withdrawal (permanent/ temporal)• Dose escalation <p>Concomitant treatment to nintedanib (excluding treatment of nintedanib-associated diarrhoea)</p> <ul style="list-style-type: none">• Receiving concomitant treatment, yes/no• Drug name, start date <p>Clinical management of nintedanib-associated diarrhoea</p> <ul style="list-style-type: none">• Receiving treatment for nintedanib-associated diarrhoea, yes/no• Type of pharmacological treatment (treatment names and start and end dates) (e.g., loperamide)• Type of non-pharmacological treatment (treatment names and start and end dates) (e.g, carob flour, zinc, probiotics, other dietary interventions, hydration)• Treatment combinations <p>Loss of follow-up, yes/no</p> <p>Adverse Drug Reactions</p>
Data sources:	<p>This study will use primary data collected by pulmonologists during presential and remote medical contacts, and secondary data obtained from hospital’s EMR. The required study information will be recorded by pulmonologists (or delegates) in an eCRF.</p>

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	<p>The pulmonologist will provide the patient with a paper patient's diary as a support document to help them remembering the information collected at each follow-up visit. This diary will not be considered a source document.</p> <p>An Investigator data collection supporting guide will be provided to investigators, summarizing the information to collect at each follow-up visit.</p>
Study size:	<p>To describe the diarrhoea management in patients with IPF and other PPF treated with nintedanib, a proportion of 0.5 is supposed (maximum indeterminacy or maximum sample size possible). Given that the proportion of patients who control the diarrhoea caused by nintedanib is unknown, the best strategy is to take maximum indeterminacy. Using this approach, a sample size of 100 patients is sufficient to estimate -with a 95% confidence and a precision of +/- 10.3%- a proportion of 0.5 with a reference population of 6337 patients, assuming a replacement rate of 10%.</p>
Data analysis:	<p>Descriptive statistics will be presented as absolute (counts) and relative frequencies (proportions) for categorical variables; and mean, standard deviation, median, 25 and 75 quartiles, and minimum, and maximum values for continuous variables.</p> <p>The comparisons of variables between the multiple follow-ups will be performed according to the distribution of the variable. Normally distributed values will be confirmed using the Shapiro Wilk test. The follow-up vs. baseline will be analysed using Student's paired t-test. For non-normal distributed values, Wilcoxon signed-rank test will be used. Categorical variables will be tested with Fisher's exact test or Chi-Squared test. P-values will be provided as descriptive representations of the data for the analysis of different subgroups and different timepoints if it is required. Full details of further analysis will be documented in the SEAP.</p>
Milestones:	<ul style="list-style-type: none"> • Final ONIS protocol: November 2023 • Ethics Committee (EC) submission: November 2023 • EC approval: December 2023 • First Competent Authority (CA) submission: December 2023 • First CA approval: January 2024 • First Patient In (start of data collection): April 2024 • Last Patient In: January 2025 • Last Patient Out (end of data collection): April 2025 • Data Base Lock: May 2025 • Final report of Study Results: November 2025 • Manuscript: January 2026

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5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	29 Oct 2024	9.1 Study Design	Non-substantial amendment Time period between Index Date and Baseline Visit increased up to 4 weeks. Baseline visit will be performed as close as possible to the index date and not later than 4 weeks after the index date).	Time period allowed between index date and baseline visit is increased from 5 days to 4 weeks to facilitate patient recruitment
	29 Oct 2024	9.2 Setting	Non-substantial amendment Time period between Index Date and Baseline Visit increased up to 4 weeks. Baseline visit will be performed as close as possible to the index date and not later than 4 weeks after the index date).	Time period allowed between index date and baseline visit is increased from 5 days to 4 weeks to facilitate patient recruitment

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Number	Date	Section of study protocol	Amendment or update	Reason
	29 Oct 2024	9.2.2 Study population Figure 2 and “The procedure for potential participants”	Non-substantial amendment Figure 2 updated with period between Index Date and Baseline Visit increased up to 4 weeks. Baseline visit will be performed as close as possible to the index date and not later than 4 weeks after the index date).	Time period allowed between index date and baseline visit is increased from 5 days to 4 weeks to facilitate patient recruitment
	29 Oct 2024	9.9 Limitations of the research methods	Information bias rephased as time period between Index Date and Baseline Visit is increased up to 4 weeks.	Time period allowed between index date and baseline visit is increased from 5 days to 4 weeks to facilitate patient recruitment

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6. MILESTONES

Milestone	Planned Date	Final date	Comments
Final ONIS protocol	November 2023	6 Nov 2023	V1
Ethics Committee (EC) submission	November 2023	15 Nov 2023	V1
EC approval	January 2024	22 Dec 2023	V2 approval
First Competent Authority (CA) submission	December 2023	15 Nov 2023	NA
First CA approval	January 2024	22 Dec 2023	NA
First Patient In (start of data collection)	April 2024	16 Jul 2024	NA
Last Patient In	January 2025	Pending	
Last Patient Out (end of data collection)	April 2025	Pending	
Data Base Lock	May 2025	Pending	
Final report of Study Results	November 2025	Pending	
Manuscript	January 2026	Pending	

All these planned dates may be modified by the administrative processing periods for study initiation and data management.

7. RATIONALE AND BACKGROUND

Interstitial lung diseases (ILDs) are a heterogeneous group of diffuse parenchymal lung disorders characterized by inflammation and fibrosis, that has a prevalence estimated to be up to 76.0 cases per 100,000 people in Europe (10, 11). The archetypal and most common fibrotic ILD is the **idiopathic pulmonary fibrosis** (IPF), which is defined as a chronic fibrosing interstitial pneumonia of unknown cause, that affects around 8.2 per 100,000 people (11, 12). In recent years, the term **progressive pulmonary fibrosis** (PPF) (also referred as progressive fibrosing ILD [PF-ILD]) has emerged to identify patients with ILDs -other than IPF- who experience worsening respiratory symptoms due to progressive radiological and physiological changes (12). These patients account for 13 to 40% of non-IPF ILDs (11, 13) and for more than 21% of all ILDs (14). Patients with IPF and other PPF have poor prognosis, and are at increased risk of mortality, with most patients dying or requiring lung transplant within two years of diagnosis (14, 15). For this population, receiving prompt treatment is critical to delay disease progression.

In the last decade, the treatments of patients with IPF and other PPF have made substantial improvements, based on novel therapies. **Nintedanib**, one of the two treatments available for IPF and the only treatment available for other PPFs, is a tyrosine kinase inhibitor (TKI) that acts by blocking tyrosine kinase enzymes of lung cells receptors (such as fibroblast growth factor receptors), inhibiting the generation of fibrotic tissue and reducing lung function decline (1, 2). Its use has been approved since January 2015 in Europe for patients with IPF, and since August 2022, for patients with systemic sclerosis associated ILD (SSc-ILD) (3) -a disease in which immune system overactivity leads to progressive scarring of the lungs- and other chronic fibrosing ILDs with a progressive phenotype (4, 16). Despite its proven benefits, nintedanib is not exempt of adverse events (AE), with the most frequent being **diarrhoea** (1-5).

Diarrhoea, defined as the passage of three or more loose or liquid stools in a 24-hour period (17) [loose or liquid stools defined as stools with a Bristol Stool Form Scale (BSFS) of 6 or 7 points (18)], is reported by 66.9% to 75.7% of nintedanib-treated patients (2-5), most frequently in those with low body mass index (19). Although most (95%) of nintedanib AEs are categorized as not serious (6), the high prevalence of diarrhoea and its potential impact on patients health status, often leads to dosage reduction or -in around 13%- to treatment discontinuation (5, 7-9), especially in female patients (5, 20). In this context and considering the limited treatment alternatives for IPF and other PPFs, it is essential to describe the real-world proportion and characteristics of patients who achieve control of nintedanib- associated diarrhoea.

In addition to dose adjustments and treatment interruptions, the management of nintedanib-associated diarrhoea is commonly based on the use of symptomatic therapies (e.g., loperamide, codeine, astringent diet, fluid, and electrolyte replacement) (5). However, to date, this AE continues to affect nintedanib adherence. In Spain, the recommendation of carob -the plant from the carob tree- to manage nintedanib-associated diarrhoea is increasing. This plant belongs to the Leguminosae family (or Fabaceae family), has been cultivated since ancient times, and has traditionally been used to treat gastrointestinal disorders (21-23). In the latest years, its primary products (i.e., flour, powder, and syrup) have been incorporated in foods, beverages, and supplements and it is increasingly recommended due to its anti-inflammatory,

antimicrobial, anti-diarrhoeal, antioxidant, antiulcer, anti-constipation, and glucose anti-absorption properties. However, there is limited evidence on the real-world use of this plant and of its association with diarrhoea outcomes in nintedanib-treated patients. In Spain, this was studied in a pilot observational study published by Alsina et al., where 87.7% of patients taking carob flour to treat nintedanib-associated diarrhoea had achieved diarrhoea control at 3-month follow-up (24).

This study aims to describe the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up among patients with IPF and other PPF who suffer a first episode of nintedanib-associated diarrhoea in real world settings in Spain. It is expected that the study findings would suggest potential alternatives to address this problem and guide future studies aiming to prove the effectiveness of anti-diarrhoeal treatments in this population.

8. RESEARCH QUESTION AND OBJECTIVES

This is an observational, non-interventional, and prospective post authorization safety study (PASS) that will describe the real-world proportion of patients that achieve nintedanib-associated diarrhoea control after 12 weeks of follow-up, in hospital settings in Spain. It will include outpatients (i.e., those attending ambulatory visits) with IPF and other PPF treated with nintedanib (150 mg bid) and having a first episode of diarrhoea after nintedanib initiation.

Main research question:

Among patients with IPF and PPF (other than IPF) treated with 150 mg bid of nintedanib suffering a first episode of nintedanib-associated diarrhoea in real-world settings in Spain, which is the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up?

Primary Objective:

To describe the proportion of patients who achieve diarrhoea control while taking a nintedanib dose of 150 mg bid at 12-week follow-up in patients with IPF and other PPF reporting a first episode of nintedanib-associated diarrhoea.

Secondary Objectives:

1. To describe the change in the proportion of patients taking the optimal nintedanib dose (150 mg bid) at 12-week follow-up referent to diarrhoea initiation.
2. To describe changes in diarrhoea indicators (BSFS and number of stools per day) and changes in body weight at 12-week follow-up referent to diarrhoea initiation.
3. To describe the proportion of patients using carob flour for the management of nintedanib-associated diarrhoea at any time from diarrhoea initiation to 12-week follow-up.
4. To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at diarrhoea initiation and 12-week follow-up.
5. To describe the nintedanib utilization pattern (occurrence of dose reductions from 150 mg bid to 100 mg bid, permanent withdrawal, and escalations from 100 mg bid to 150 mg bid) in the study population from diarrhoea initiation to 12-week follow-up.

Further objectives:

1. To describe changes in diarrhoea indicators (BSFS and number of stools per day) and changes in body weight at 6-week follow-up referent to diarrhoea initiation.
2. To describe the number of patients who do not receive treatment for nintedanib-associated diarrhoea in all the study period (i.e., from diarrhoea initiation to 12-week follow-up).
3. To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at 6-week follow-up referent to diarrhoea initiation.
4. To describe the counts of different treatment combinations (e.g., loperamide + carob flour) used at least once for the management of nintedanib-associated diarrhoea from diarrhoea initiation to 12-week follow-up.
5. To describe the occurrence of at least one episode of persistent diarrhoea (lasting ≥ 14 days) and the number of persistent diarrhoea episodes in the study population from diarrhoea initiation to 12-week follow-up.
6. To describe the duration of the first nintedanib-associated diarrhoea episode.
7. To describe the time from nintedanib initiation to the first nintedanib-associated diarrhoea episode.
8. To describe the occurrence of at least one nintedanib temporary interruption from diarrhoea initiation to 12-week follow-up.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is an observational, non-interventional, multicentre, and prospective, real-world PASS, that will describe the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up in patients with IPF and other PPF treated with nintedanib in hospital settings in Spain. It will be conducted using primary data collected during routine medical contacts, which will be complemented with secondary data extracted from electronic medical records (EMR) and recorded by pulmonologists (or delegates) in an electronic case report form (eCRF). Patients will be competitively recruited during a first face-to-face consultation with their pulmonologists due to a first episode of diarrhoea after the initiation of nintedanib (see section **9.2.2 Study population**).

Study baseline, defined as the first face-to-face visit of patients with their pulmonologists due to a reported first episode of diarrhoea (when the pulmonologist will collect data related to the day of diarrhoea initiation), will be conducted as close as possible to index date, and not later than 4 weeks after the diarrhoea initiation (index date) reported by the patient. Patients will be followed 3, 6, and 12 weeks remotely or presential after the baseline visit ([Figure 1](#)). These time points were selected based on a previous pilot study (24) in which patients were followed-up around 3 months to evaluate the association of nintedanib-associated diarrhoea treatment and diarrhoea outcomes.

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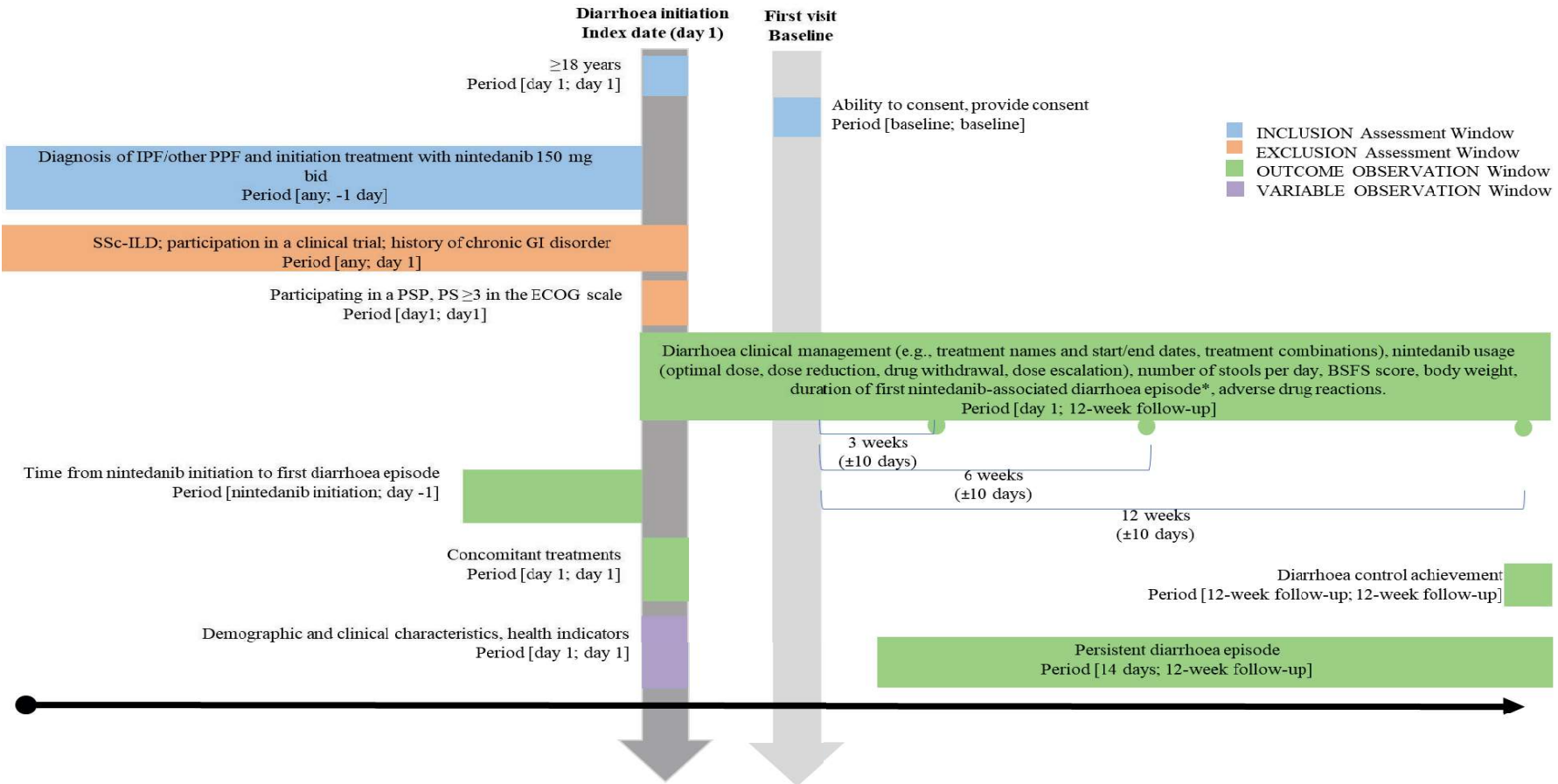
The decision to conduct an observational study emerged due to the lack of evidence regarding the management of diarrhoea in patients treated with nintedanib in Spain. Considering that the clinical management of diarrhoea (which might include conventional antidiarrheic drugs, but also dietary interventions) and diarrhoea outcomes (e.g., diarrhoea duration and intensity) are not always registered as structured data (e.g., using ATC codes) or in detail to obtain conclusions, a prospective design was chosen to allow a more accurate, comprehensive, and homogenic registration of these variables.

This is a non-interventional study -as defined by the Clinical Trial Directive (DIR 2001/20/EC) of the European Parliament- that will be conducted following the guidelines of the International Council for Harmonization (ICH) Good Pharmacoeepidemiology Practice (GPP). It is sponsored by Boehringer Ingelheim (BI) and managed by [REDACTED] clinical research organization (CRO). As this is a non-interventional study, the decision to prescribe nintedanib and any other intervention will be made under the sole responsibility of the healthcare professional independently from the decision to include the subject in the study. This decision should be made in accordance with routine/standard clinical practice at the investigational site. In addition, the strategy to manage nintedanib-associated diarrhoea will be decided according to the usual clinical practice in each participating site. In usual clinical practice, diarrhoea management might include diet modifications including the use of carob flour, hydration, treatment with loperamide or other anti-diarrhoeal medications, and nintedanib treatment modifications (e.g., dose reductions and/or temporary/permanent interruptions).

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Figure 1: Study design



Abbreviations: ECOG= Eastern Cooperative Oncology Group scale; IPF= idiopathic pulmonary fibrosis; PPF= progressive pulmonary fibrosis; PSP= Patient Support Programme; GI= gastrointestinal; PS= performance status; SSc-ILD= systemic sclerosis associated interstitial lung disease.

Vertical arrow indicates patient timeline and horizontal arrow indicates dataset timeline.

* The duration of the first nintedanib-associated diarrhoea episode will be evaluated from the first occurrence of diarrhoea until end of diarrhoea.

Loss of follow-up is not included in the image.

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9.2 SETTING

This study will include patients diagnosed with IPF and other PPF who have a first face-to-face visit with their pulmonologist (study baseline) due to a first episode of diarrhoea while being treated with 150 mg bid of nintedanib in hospital settings in Spain. Recruitment will last approximately 6 months (depending on the initiation date in each site) and the study period will last approximately 9 months (from the inclusion of the first patient to the last follow-up visit of the last patient). The 6 months of recruitment could be extended if target sample size is not reached.

Index date will be defined as the date of diarrhoea initiation and study baseline will be defined as the first face-to-face patient visit with their pulmonologist due to a first episode of diarrhoea after the initiation of nintedanib. Baseline visit will be performed as close as possible to the index date and not later than 4 weeks after the index date).

Patients will be assessed at study baseline and at 3-, 6-, and 12-week follow-up from baseline; and will be followed until death, loss of follow-up, or end of study follow-up (12 weeks), whichever comes first. Patients who withdraw nintedanib will be still followed until the 12-week follow-up.

9.2.1 Study sites

The selection of study sites will aim to obtain a representative study population that will reflect the routine management of nintedanib-associated diarrhoea in patients with IPF/other PPF. For this purpose, this study will include approximately 20 sites located in at least 5 Spanish regions. Eligible sites will be expert and non-expert hospitals, managing at least 1 new patient treated with 150 mg bid of nintedanib and reporting a first episode of diarrhoea each month.

The sites selection was performed by applying a feasibility questionnaire that determined whether the site had adequate facilities, qualified pulmonologists, the potential to meet recruitment targets, and to demonstrate on-time compliance with regulatory requirements. The recruitment will be competitive although it is expected to include approximately 3 to 5 patients in each study centre. If this target is not reached during the recruitment period, the inclusion of additional sites and/or the increase in the maximum number of patients per site may be considered. Permission to include more than 5 patients per site must be obtained from the sponsor.

9.2.1.1 Managing Site and Physician/Investigator Selection, Contracting and Training**Investigators selection:**

Investigators will be pulmonologists working in the included study centres who will be identified in a list provided from BI to [REDACTED] Information. [REDACTED] Eligible pulmonologists will be those providing medical attention to ≥ 1 patient with nintedanib-associated diarrhoea per month.

Sites will be identified from several sources:

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- Suggestions from Boehringer internal colleagues.
- BI local database containing investigator and site participation and performance in previous BI-sponsored local ONIS.

A comprehensive site list will be developed well ahead of protocol finalization.

Conduct site feasibility questionnaire:

To ensure that the most appropriate sites will participate in the study, a Site Feasibility Questionnaire (SFQ) will be used to ask sites about their interest and ability to conduct the study. The BI Medical Scientific Liaison (MSLs) will contact the identified sites for reviewing and filling out the SFQ with the answers provided by the investigator. The SFQ will contain a section with brief information about the study for the investigator and other sections with questions focused on determining if the site and the study site team is able to participate in the study.

Considerations when selecting a site:

From an initial list of approximately 30 identified potential sites in at least 5 Spanish regions, around 20 sites will be selected to participate in the study. After completing the SFQ, below are some criteria for selecting a site:

- Ability to conduct the study
- Representativeness
- Inclusion rate
- Resources
- Competitive trials and/or studies
- Expert and non-expert sites in ILD management

Moreover, BI team will consider identifying more sites than needed, including “back-up sites” in case site(s) drop out or more sites are needed in case inclusion rates are lower than expected.

The list with the selected sites will be verified with BI study team in terms of the target physician specialties and site types that reflect standard of care for the indication under study.

The investigators will be informed by BI about the final decision of being/not being selected for the study.

Obtain signed confidentiality agreement (CDA) and Privacy Note:

Before sharing the complete ONIS protocol to the selected sites/investigators, a confidentiality agreement (CDA) and a privacy notice with the investigators will be signed.

Investigator/site confirmation:

Once the investigators have read the ONIS protocol, they will reconfirm their ability to conduct the study, to achieve the recruitment commitment of each site, and their interest in participating in the study.

The final list will contain the investigators/sites that will participate in the study. This comprehensive final site/investigator list, including contact information will be shared with [REDACTED].

9.2.2 Study population

This study will include patients diagnosed with IPF and other PPF, as registered in their EMR at least one day before the initiation of the first nintedanib-associated diarrhoea episode. Eligible patients will be those being treated with nintedanib (having started treatment at least one day before diarrhoea initiation, at a dose of 150 mg twice per day [bid]) having a first face-to-face visit with their pulmonologists due to a first diarrhoea episode after nintedanib initiation, during the study recruitment period ([Table 1](#)). To ensure sample representativeness, participants will be recruited in multiple study centres across Spain and a maximum number of participants per hospital will be established.

Identification of potential participants:

Potential participants, who could eventually meet the study selection criteria, will be:

1. Patients receiving a first nintedanib prescription by pulmonologists or
2. Patients being treated with nintedanib and have not presented any diarrhoea episode since nintedanib initiation.

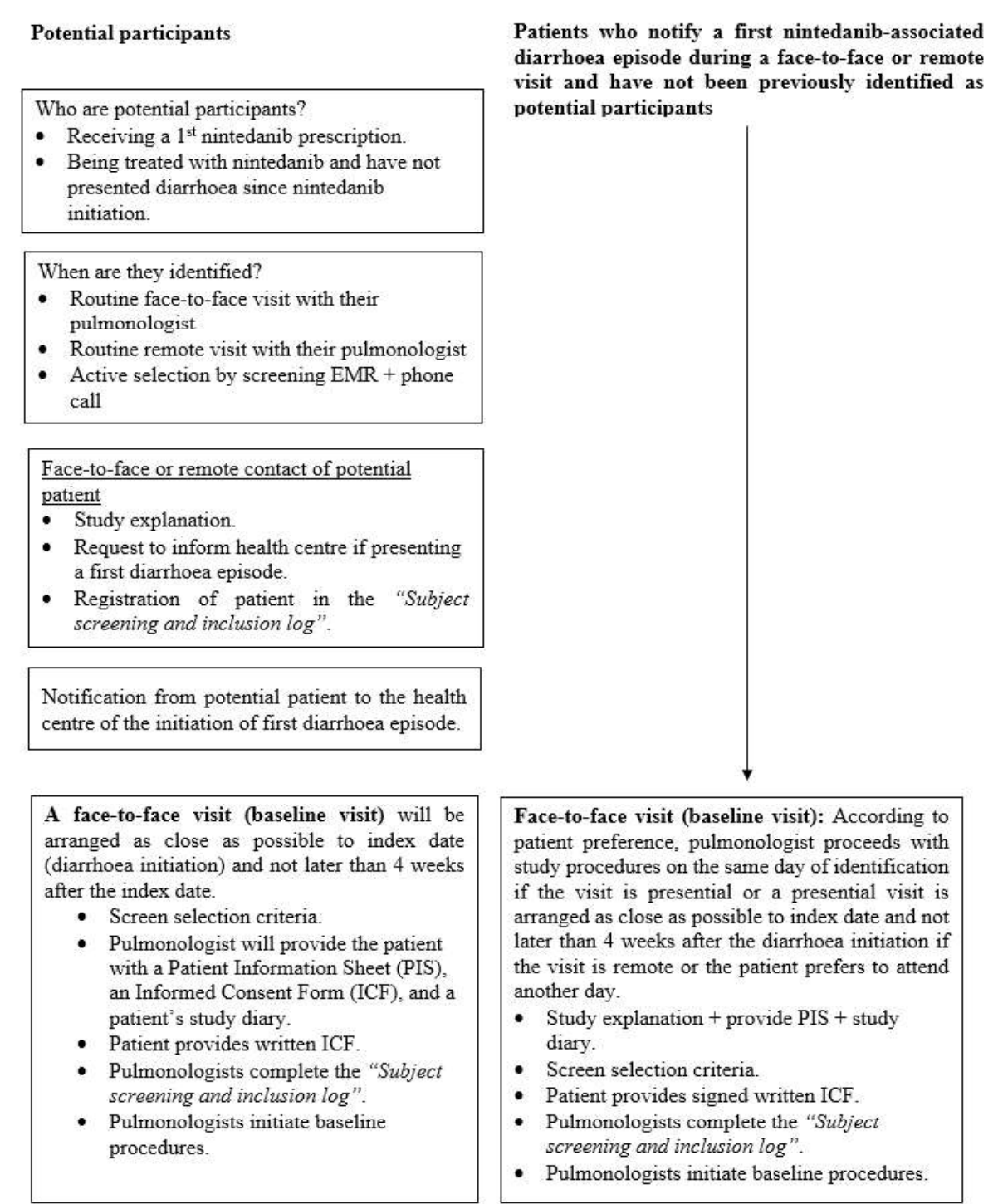
Potential participants will be identified through one of the following ways:

1. During a routine face-to-face visit with their pulmonologist.
2. During a routine remote visit with their pulmonologist.
3. During an active selection and calling of potential participants, identified by screening EMR, by the pulmonologist.

Recruitment, providing informed consent, and initiation of baseline visit:

The pulmonologist will invite to participate in the study those patients previously identified as potential participants and those patients not previously identified as potential participants. In both cases, patients will be invited to participate after patients' report of a first diarrhoea episode while taking nintedanib ([Figure 2](#)).

Figure 2: Steps from participants recruitment to study baseline



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The procedure for potential participants will be as follows:

1. During a face-to-face or remote contact with a potential participant, the pulmonologist will explain the study to them, and they will be asked to inform the health centre if presenting a first diarrhoea episode.
2. Once the study has been explained to potential participants, the pulmonologist will register potential participants in the *Screening section* of the “*Subject screening and inclusion log*”.
3. Potential participants will inform the health centre about the initiation of a first episode of diarrhoea during treatment with nintedanib. Health centre will inform the potential participants that the pulmonologist will perform a face-to face visit with them as close as possible to the date of diarrhoea initiation and no later than 4 weeks after diarrhoea initiation.
4. Pulmonologists will arrange a presential visit with the potential participants to confirm if the potential participant meets the study selection criteria as soon as possible to index date and not later than 4 weeks after the diarrhoea initiation.
5. If a potential participant meets the selection criteria and accepts to participate in the study, the pulmonologist will provide the patient with a Patient Information Sheet (PIS), an Informed Consent Form (ICF) and a patient’s study diary. The patients will be included in the study once they provide the signed written consent. The patient will receive a copy of the signed informed consent form. This visit, in which the consent is provided, will be considered as baseline visit and all data related to onset of diarrhoea will be collected (see [Table 2](#)). The pulmonologist will record in the patient's EMR the date when the patient has signed the informed consent form.
6. Pulmonologist will complete the inclusion section of the “*Subject screening and inclusion log*” confirming the participation of patient in the study.

The procedure for patients who notify a first diarrhoea episode associated with nintedanib during a face-to-face or remote visit with their pulmonologist and have not previously been identified as potential participants, will be as follows:

1. The pulmonologist will explain the study to the patient during this visit and will confirm if patient meets screening selection criteria.
2. If it is a face-to face visit and patient accepts to participate, the pulmonologist will give to the patient the PIS, the ICF and the paper patient’s diary and depending on patient preferences, the ICF could be signed, and study baseline visit could be performed on the same day or a new presential visit can be scheduled as close as possible to the index date and not later than 4 weeks after diarrhoea initiation. The patient will receive a copy of the informed consent signed.

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3. If it is a remote visit and the patient accepts to participate, the pulmonologist will arrange a presential visit as close as possible to index date and not later than 4 weeks after diarrhoea initiation. During this visit, considered as baseline visit, the pulmonologist will give to the patient the PIS, the ICF and the paper patient's diary. The patient will sign the ICF and will receive a copy of the signed ICF.
4. In both cases, pulmonologists will complete the inclusion section of the "*Subject screening and inclusion log*". In all cases, the physician will document in the patient's EMR the date of signing the paper consent.

Selection criteria:

The study will include patients diagnosed with IPF and other PPF. Idiopathic pulmonary fibrosis is defined as a chronic fibrosing interstitial pneumonia of unknown cause while the term PPF refers to patients with ILDs -other than IPF- who have at least two of the following three criteria: worsening of respiratory symptoms, radiological progression, and physiological progression occurring during the past year (12). In this study, these diagnoses will be defined as having an IPF or PPF diagnose confirmed by a physician, as registered in the EMR.

The study will exclude patients with SSc-ILD. This decision was based on the fact that nearly 90% of patients with Systemic Sclerosis (SSc) present gastrointestinal manifestations affecting the oesophagus, stomach, small and large bowels, liver, and pancreas (25), leading to symptoms such as dyspepsia, nausea, vomiting, abdominal bloating/distension, and faecal incontinence (26). Therefore, in these patients, the management of nintedanib-related diarrhoea and its association with diarrhoea outcomes likely differs from the rest of patients presenting PPF.

Table 1: Selection criteria

Inclusion criteria/definition
1. Adults (≥18 years old) at diarrhoea initiation.
2. Ability to consent and to conduct all procedures of the study, as judged by the study investigator, and agreeing to participate providing informed consent at baseline.
3. Diagnosis of IPF or PPF (other than IPF), as registered in EMR using free text or ICD codes (ICD-9 and/or ICD-10), at least 1 day before diarrhoea initiation.
4. Being treated with 150 mg bid of nintedanib when initiating diarrhoea symptoms, defined as having a nintedanib ATC code (L01EX09) or the molecule/commercial name registered in the EMR, for at least 1 day before diarrhoea initiation.
5. First pulmonologist consultation (face-to-face) at the time of recruitment due to a first diarrhoea episode as defined by the pulmonologist since nintedanib initiation. Diarrhoea defined as the passage of three or more loose or liquid stools in a 24- hour period (17) (loose or liquid stools defined as stools with a BSFS of 6 or 7 points (18)).
Exclusion criteria
1. Patients diagnosed with systemic sclerosis associated interstitial lung disease (SSc-ILD) as registered in EMR using free text or ICD codes (ICD-9 and ICD-10). Referent to any time before or at diarrhoea initiation.
2. Participation in any clinical trial including a drug or device at any time before or at diarrhoea initiation.
3. Participation in any Patient Support Programme (PSP) at diarrhoea initiation.
4. Having history of chronic gastrointestinal disorder (e.g., inflammatory bowel disease or the short gut syndrome), pancreatic dysfunction/insufficiency, or colon cancer; due to the likelihood of faecal incontinence. Referent to any time before or at diarrhoea initiation.
5. Having a performance status (PS) ≥3 points on the ECOG scale at diarrhoea initiation, due to the likelihood of faecal incontinence.

Abbreviations: ATC= anatomical therapeutic chemical; ECOG= Eastern Cooperative Oncology Group scale; EMR= electronic medical record; ICD= International Statistical Classification of Diseases and Related Health Problems; IPF= idiopathic pulmonary fibrosis; PPF= progressive pulmonary fibrosis; Baseline: first pulmonologist visit (face-to-face) due to a first episode of diarrhoea after nintedanib initiation.

9.2.3 Study visits

Patients will be assessed at study baseline (date of the first pulmonologist presential visit for study data collection) and at 3-, 6-, and 12-week follow-up after baseline visit during face-to-face or remote consultations (e.g., by phone). Due to the real-world variability in the timing of medical visits/contacts, flexible time windows will be stablished (±10 days).

Data collection schedule and method:

The variables/group of variables will be collected during the period of study (from baseline to 12-week follow-up) to meet the study objectives (Table 2).

A patient’s diary will be provided to all included patients. This diary will serve as a support document, that patients can use to register the information that will be later collected at each

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follow-up visit and will not be considered a source document. This information will include, at least:

- Diarrhoea-related information.
- Information on diarrhoea treatment.
- Nintedanib pattern of use.

Table 2: Data collection schedule and data collection method

	Baseline (Presential)	Follow-up contacts (Presential or remote)			Method
		3- week (± 10 days)	6- week (± 10 days)	12- week (± 10 days)	
Obtaining Informed Consent	x				A signed ICF paper copy will be provided to all patients. Written informed consent date will be documented in the EMR.
Eligibility confirmation	x				Obtained from EMR and/or reported by patients during first study contact.
Demographic/clinical characteristics <ul style="list-style-type: none">• Age, years• Sex• Race/ ethnicity• Body mass index (or weight and hight), kg/m²• Smoking status• Pulmonary disease: IPF/other PPF (type of PPF) and date of diagnosis• Comorbidities and date of diagnosis<ul style="list-style-type: none">○ Arterial hypertension○ Diabetes○ Gastroesophageal reflux○ Coronary heart disease○ Sleep apnoea-hypopnea syndrome○ Heart disease○ Asthma○ Chronic bronchitis○ Chronic Obstructive Pulmonary Disease○ Emphysema○ Lung cancer	x*				Obtained from EMR, reported by patients during study contact, and/or directly measured by the pulmonologist (e.g., weight).

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○ Other relevant comorbidities: names and dates					
Health indicators <ul style="list-style-type: none"> FVC, litres Diffusing Capacity of Lung for Carbon Monoxide, (% predicted) ECOG scale, score 	x*				Obtained from EMR, reported by patients during study contact, and/or directly measured by the pulmonologist (e.g., FVC).
Diarrhoea control achievement, yes/no (<3 loose or liquid stools in a 24-hour period, while being treated with 150 mg bid of nintedanib)				x	Obtained from EMR and/or reported by patient (with support of his/her diary) during study contact
Diarrhoea indicators and body weight <ul style="list-style-type: none"> Number of stools per day BSFS score Body weight, kilograms 	x*	x	x	x	Obtained from EMR, reported by patient (with support of his/her diary) during study contact, and/or directly measured by the pulmonologist.
Persistent diarrhoea episode (≥ 3 loose or liquid stools in a 24-hour period for a total duration ≥ 14 days) <ul style="list-style-type: none"> Occurrence of at least one persistent diarrhoea episode, yes/no Number of persistent diarrhoea episodes 				x	Obtained from EMR and/or reported by patient (with support of his/her diary) during study contact.
Duration of first nintedanib-associated diarrhoea episode, days		x**	x**	x**	Obtained from EMR and/or reported by patient (with support of his/her diary, if available at baseline) during study contact.
Time from nintedanib initiation to the first diarrhoea episode, days	x				Obtained from EMR and/or reported by patient (with support of

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					his/her diary, if available at baseline) during study contact.
Nintedanib use <ul style="list-style-type: none"> Optimal nintedanib dose Dose reductions Drug withdrawal (permanent/temporal) Dose escalation 	x*	x	x	x	Obtained from EMR and/or reported by patient (with support of his/her diary) during study contacts.
Concomitant treatment to nintedanib (excluding treatment of nintedanib-associated diarrhoea) <ul style="list-style-type: none"> Receiving concomitant treatment, yes/no Drug name, start date 	x*				Obtained from EMR and/or reported by patient during study contact.
Clinical management of nintedanib-associated diarrhoea <ul style="list-style-type: none"> Receiving treatment nintedanib-associated diarrhoea, yes/no. Type of pharmacological treatment (drug names and start and end dates) (e.g., loperamide). Type of non-pharmacological treatment (treatment names and start and end dates) (e.g, carob flour, zinc, probiotics, other dietary interventions, hydration). Treatment combinations. 	x*	x	x	x	Obtained from EMR and/or reported by patient (with support of his/her diary). during study contact.
Loss of follow-up, yes/no.		x	x	x	Extracted from EMR and confirmed during study contacts.
Adverse Drug Reactions	x	x	x	x	Reported by patient (with or without support of his/her diary) during the study period.

Abbreviations: BSFS= Bristol Stool Form Scale; ECOG= Eastern Cooperative Oncology Group scale; EMR= electronic medical record; FVC= Forced vital capacity; IPF= idiopathic pulmonary fibrosis; PPF= progressive pulmonary fibrosis.

* Measured referent to the day of diarrhoea initiation.

** To collect only if not collected in previous visits.

9.2.4 Study discontinuation

Boehringer Ingelheim reserves the right to discontinue the study at any time, in all or at a particular study site, for the following reasons:

- 1. Failure to meet expected inclusion goals in all or at a particular study site.
- 2. Emergence of any effectiveness/ safety information that could significantly affect continuation of the study, or any other administrative reasons.
- 3. Violation of GPP, the study protocol, or the contract by a study site, investigator, or research collaborator, disturbing the appropriate conduct of the study.

The investigator/ study site/ research collaborator will be reimbursed for reasonable expenses incurred in case of study/ site termination (except in case of the third reason).

9.3 VARIABLES

A summary of variables related to main objectives are described in [Table 3](#).

Table 3: Main variables related to study objectives

Diarrhoea control achievement, yes/no (<3 loose or liquid stools in a 24-hour period while being treated with 150 mg bid of nintedanib)
Diarrhoea indicators and body weight <ul style="list-style-type: none">• Number of stools per day• BSFS score• Body weight, kilograms
Nintedanib use <ul style="list-style-type: none">• Optimal nintedanib dose• Dose reductions• Drug withdrawal (permanent/ temporal)• Dose escalation
Clinical management of nintedanib-associated diarrhoea <ul style="list-style-type: none">• Receiving treatment nintedanib-associated diarrhoea, yes/no.• Type of pharmacological treatment (drug names and start and end dates) (e.g., loperamide).• Type of non-pharmacological treatment (treatment names and start and end dates) (e.g, carob flour, zinc, probiotics, other dietary interventions, hydration).• Treatment combinations.
Persistent diarrhoea (≥3 loose or liquid stools in a 24-hour period for a total duration of ≥14 days) <ul style="list-style-type: none">• Occurrence of at least one persistent diarrhoea episode, yes/no• Number of persistent diarrhoea episodes
Time from nintedanib initiation to the first diarrhoea episode, days
Duration of first nintedanib-associated diarrhoea episode, days

9.3.1 Exposures

Effect assessment of nintedanib and diarrhoea treatments is not an objective of this observational study. Patients will have been already treated with nintedanib before being included in the study. Prescription of nintedanib and diarrhoea treatments will have been done under the sole responsibility of the healthcare professional and independently of the present study. Nintedanib and diarrhoea treatments pattern of use will be collected (e.g., dose reduction, escalation, interruptions, withdrawals) with descriptive purposes. No intervention, either diagnostic or therapeutic, will be applied to patients other than that used for routine clinical practice.

9.3.2 Outcomes

The study outcomes are detailed in [Table 4](#). Diarrhoea will be defined as the passage of three or more loose or liquid stools in a 24- hour period (18) (loose or liquid stools defined as stools with a BSFS of 6 or 7 points (17)); and a diarrhoea episode will be defined considering that two diarrhoea episodes are separated by at least 7 days without any diarrhoea.

The BSFS is a 7-point ordinal scale of stool types used in clinical practice and research (18, 27). It ranges from the hardest (1 point or type 1) to the softest stool form (7 points or type 7), with 6 and 7 points considered abnormally loose/liquid stools. Persistent diarrhoea will be defined as a diarrhoea episode lasting ≥14 days (17, 28, 30).

Table 4. Outcomes of study according to study objectives

	Primary objective	Primary Outcome name
1	To describe the proportion of patients who achieve diarrhoea control while taking a nintedanib dose of 150 mg bid at 12-week follow up in patients with IPF and other PPF reporting a first episode of nintedanib-associated diarrhoea.	1. Achievement of diarrhoea control (yes/no), defined as the passage of less than 3 loose or liquid stools in a 24-hour period (loose or liquid stools defined as stools with a BSFS of 6 or 7 points while being treated with 150 mg bid of nintedanib, at 12-week follow-up. Safety Issue: Yes
	Secondary objective	Secondary Outcome name
1	To describe the change in the proportion of patients taking the optimal nintedanib dose (150 mg bid) at 12-week follow-up referent to diarrhoea initiation.	1. Absolute change in the proportion of patients taking optimal nintedanib dose (150 mg bid) at 12-week follow-up referent to diarrhoea initiation. Safety Issue: No

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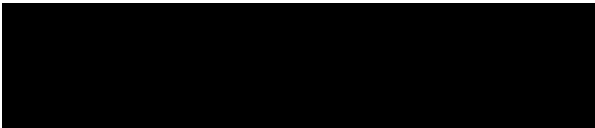
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2	To describe changes in diarrhoea indicators (BSFS and number of stools per day) and changes in body weight at 12-week follow-up referent to diarrhoea initiation.	2. Absolute change in BSFS score at week 12 follow-up referent to diarrhoea initiation. 3. Absolute change in number of stools per day at 12-week follow-up referent to diarrhoea initiation. 4. Absolute change in current body weight (in kilograms) at 12-week follow-up referent to diarrhoea initiation. Safety Issue: Yes
	Secondary objective	Secondary Outcome name
3	To describe the proportion of patients using carob flour for the management of nintedanib-associated diarrhoea at any time from diarrhoea initiation to 12-week follow-up.	5. Proportion of patients using carob flour for the treatment of nintedanib-associated diarrhoea at any time from diarrhoea initiation to 12-week follow-up. Safety Issue: No
4	To describe the type of treatment of nintedanib-associated diarrhoea (e.g., loperamide, or dietary intervention such as carob flour) at diarrhoea initiation and 12-week follow-up.	6. Number of patients per treatment category for nintedanib-associated diarrhoea at diarrhoea initiation. 7. Number of patients per treatment category for nintedanib-associated diarrhoea at 12-week follow-up. Treatment categories of nintedanib-associated diarrhoea could include pharmacological treatments (e.g., loperamide) or non-pharmacological treatment (e.g., carob flour, zinc, probiotics, other dietary interventions, hydration). Safety Issue: No.
5	To describe the nintedanib utilization pattern (occurrence of dose reductions from 150 mg bid to 100 mg bid, permanent withdrawal, and escalations from 100 mg bid to 150 mg bid) in the study population from diarrhoea initiation to 12-week follow-up.	8. Occurrence of at least one dose reduction (yes/no), defined as reduction of nintedanib dose from 150 mg bid to 100 mg bid, from diarrhoea initiation to 12-week follow-up. 9. Occurrence of permanent withdrawal, defined as discontinuing 150 mg bid or 100 mg bid of nintedanib and not reintroducing it before the 12-week follow-up). 10. Occurrence of at least one dose escalation (yes/no), defined as an increase of nintedanib dose from 100 mg bid to 150 mg bid from diarrhoea initiation to 12-week follow-up. Safety Issue: No.



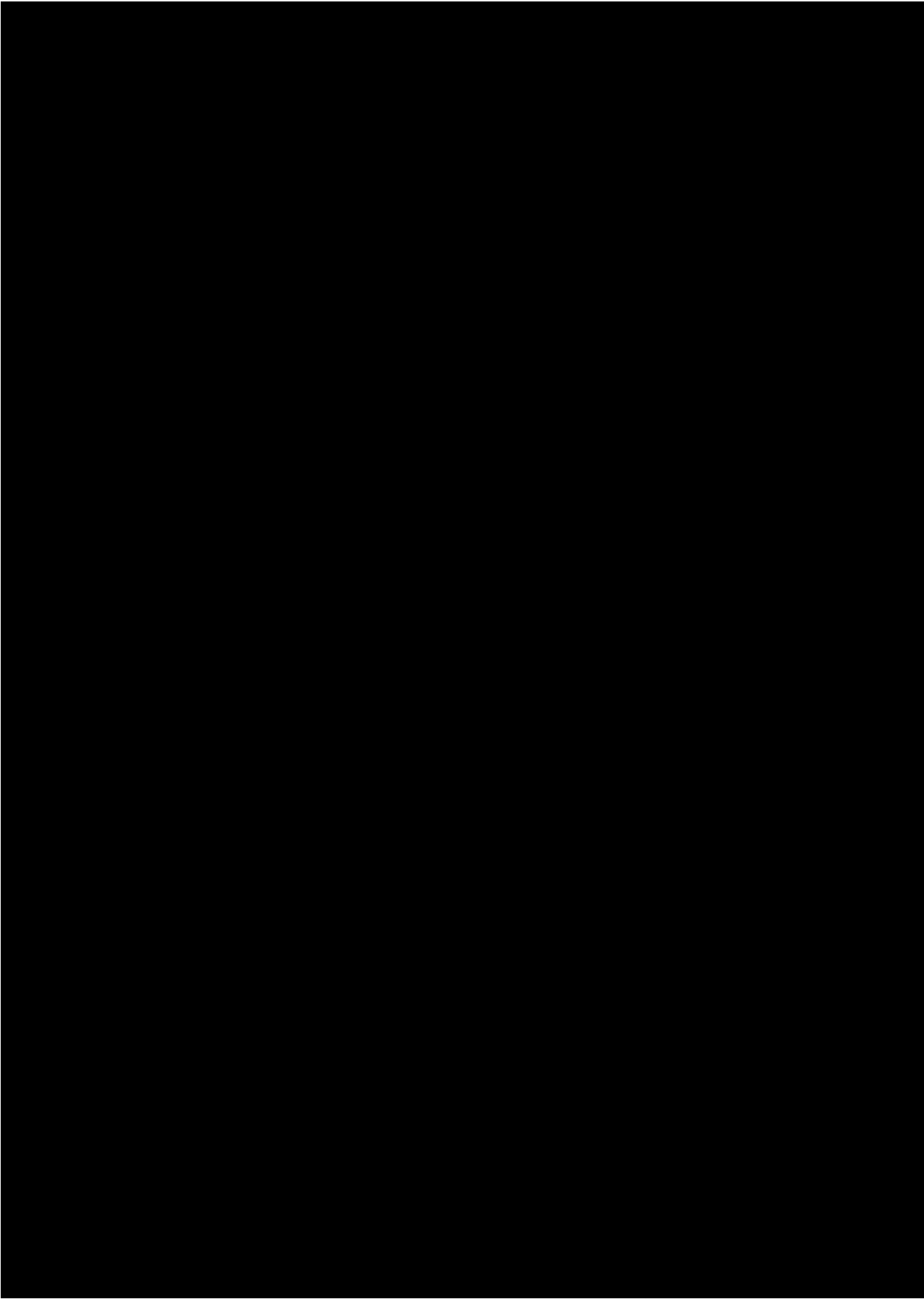
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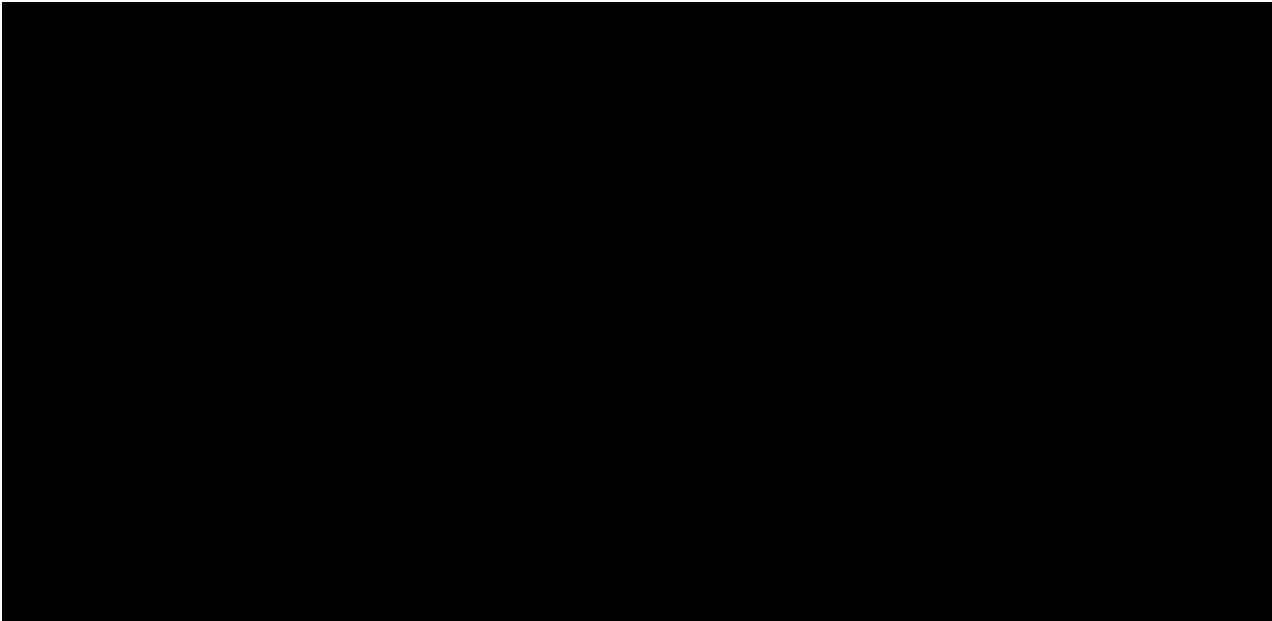
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9.3.3 Covariates

The covariates analysed in the study are described in [Table 6](#).

Table 6: Covariates to describe the study population

<p>Demographic and clinical characteristics of the study population at diarrhoea initiation.</p> <ul style="list-style-type: none">• Age: continues variable, in years.• Sex: categorized in male/ female.• Race/ ethnicity: categorized in Asian, black, Latino, white, and other.• Body mass index: calculated weight in kilograms divided by the square of body height in meters (kg/m²).• Smoking status: categorized in former smoker/ current smoker/ no smoker.• Pulmonary disease: IPF/PPF (type of PPF) and date of diagnosis (31).• Comorbidities and date of diagnosis<ul style="list-style-type: none">○ Arterial hypertension○ Diabetes○ Gastroesophageal reflux○ Coronary heart disease○ Sleep apnoea-hypopnea syndrome○ Heart disease○ Asthma○ Chronic bronchitis○ Chronic Obstructive Pulmonary Disease○ Emphysema○ Lung cancer○ Other relevant comorbidities: names and dates• Health indicators.<ul style="list-style-type: none">○ FVC in litres (last measure available).○ Diffusing Capacity of Lung for Carbon Monoxide (% predicted) (last measure available).○ ECOG scale, to assess PS. <p>Concomitant treatment at diarrhoea initiation (excluding treatment of nintedanib-associated diarrhoea)</p> <ul style="list-style-type: none">• Receiving concomitant treatment, yes/no.• Drug name, start date.

Loss of follow-up, yes/ no.
Adverse Drug Reactions

Abbreviations: ECOG= Eastern Cooperative Oncology Group scale; EMR= electronic medical record; FVC= Forced vital capacity; IPF= idiopathic pulmonary fibrosis; PPF= progressive pulmonary fibrosis; PS: Performance Status.

9.4 DATA SOURCES

This study will use primary data collected by pulmonologists during presential or remote medical contacts, and secondary data obtained from hospital’s EMR.

Primary data collection

The required study information will be recorded by pulmonologists (or delegates) in an eCRF. It is expected that the data collected in the eCRF will match the data in the patient medical charts maintained by the study sites.

The pulmonologist will provide the patient with a paper patient’s diary as a support document to help the patients remembering the information collected at each follow-up. The patient’s diary will not be considered a source document and therefore, it will not be collected nor kept by the study site.

An Investigator data collection supporting guide will be provided to investigators, summarizing the information to collect in each study time-point.

9.5 STUDY SIZE

This study will be carried out in Spain, a country with a total population of 47.4 million people. Given that IPF affects around 8.2 per 100,000 people (11, 12), ILD affects up to 76.0 cases per 100,000 people in Europe (10, 11), and PPF affects up to 40% of non-IPF ILDs (11, 13), it is estimated that there is a total of 3,887 patients diagnosed with IPF and 12,855 diagnosed with PPF in Spain. Considering that approximately 50% of these patients are treated with nintedanib (9), and that up to 75.7% present diarrhoea as a result of the treatment (2-5), it is estimated that 6,337 patients in Spain are diagnosed with IPF or other PPF and present nintedanib-associated diarrhoea.

To describe the diarrhoea management in patients with IPF and other PPF treated with nintedanib, a proportion of 0.5 is supposed (maximum indeterminacy or maximum sample size possible). Given that the proportion of patients who control the diarrhoea caused by nintedanib is unknown, the best strategy is to take maximum indeterminacy. Using this approach, a sample size of 100 is sufficient to estimate -with a 95% confidence and a precision of +/- 10.3%- a proportion of 0.5 with a reference population of 6337 patients, assuming a replacement rate of 10%.

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9.6 DATA MANAGEMENT

The data management plan is summarized below. Full details of the data management plan will be included in a separate ONIS-Data Management and Review Plan (ONIS-DMRP). This ONIS-DMRP will be written by [REDACTED] and approved by BI before the design of the study database is finalized.

During the study completion, data will be collected by study sites investigators (pulmonologists or delegates) during direct interviews with patients and through EMR review. Then, data will be entered to an eCRF. Investigators will be responsible for the integrity of the data reported. Each participating site will have access exclusively to the data entered in its own site.

All sites will be fully trained on using the online data capture system, including eCRF completion, guidelines, and support files. Investigators and site personnel will be able to access their account with a username and a password. All eCRFs should be completed by designated trained personnel. The eCRF will be reviewed, electronically signed, and dated by the Principal Investigator. All changes or corrections to eCRFs will be documented in an audit trail and an adequate explanation will be required.

All investigators will be required to follow local laws and regulations and institutional practices for document retention.

All information about this observational study and individual participant medical information resulting from this study are considered confidential, and disclosure to third parties is prohibited except for regulatory authorities, and as applicable by law. Publications may result from this study, but in no case patient confidentiality will be compromised.

Data in the eCRF system will be kept in a central location and all data will be transmitted to a central database. The eCRF is a web-based application accessible on any computer with an Internet connection. The Hypertext Transfer Protocol Secure (HTTPS) with a 128-bit Secure Sockets Layer (SSL) certificate will be used for web communication. This will ensure the confidentiality of the communications between the servers and the investigators' computers by encrypting all the transmitted data ("secure connection"). The SSL technology implemented ensures that all the data transferred to the server from the CRO database will be encoded and protected from external attacks. Audit trail follow-up will ensure monitoring of any movement of the saved data. The information recorded for each value stored in the database includes event date, responsible party, variable, old value, new value, and type of step taken (data creation, updating or deletion). This audit process provides an additional safety mechanism to ensure the security of the data stored and could also be useful for the site staff in answering questions regarding data entry.

BI will perform oversight of the data management of this study, including approval of the ONIS-DMRP, that will be written by [REDACTED] will produce eCRF specifications for the study, based on the study initiator's templates, including quality checking to be performed on the data.

All the information entered in the eCRF must be traceable to the original documents in the patient's EMR. The investigator must keep the original ICF (signed by the patient), and the patient will be given a signed copy.

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All statistical analyses will be conducted using SAS Guide Enterprise (version 7.15 or higher) or using R (version 4.1.1) and R studio (version 1.4.1717).

9.7 DATA ANALYSIS

The statistical analysis plan for the study is summarized below. Full details of the statistical analysis plan will be documented in the Statistical and Epidemiological Analysis Plan (SEAP), which will be written by the CRO and finalized before the end of data collection.

9.7.1 Main analysis

Descriptive statistics will be presented as absolute (counts) and relative frequencies (proportions) for categorical variables; and mean, standard deviation, median, 25 and 75 quartiles, and minimum, and maximum values for continuous variables.

The comparisons of variables between the multiple follow-ups will be performed according to the distribution of the variable. Normally distributed values will be confirmed using the Shapiro Wilk test. The follow-up vs. baseline for continuous variables will be analysed using Student's paired t-test. For non-normal distributed values, Wilcoxon signed-rank test will be used. Categorical variables will be tested with Fisher's exact test when low frequencies, or with Chi-Squared test. P-values will be provided as descriptive representations of the data for the analysis of different subgroups and different timepoints if it is required. Full details of further analysis will be documented in the SEAP.

9.7.3 Safety Analysis

Adverse Drug Reactions (ADRs) will be notified to Pharmacovigilance according to the protocol (**section 11**) and they will be described according to full details documented in the SEAP.

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. Full details will be documented in the ONIS-DMRP.

To ensure data quality and integrity, quality controls and other procedures will be performed. These procedures will be conducted according to the Standard Operating Procedures (SOPs) from BI and/or [REDACTED] (depending on which one applies in each case), and according to the ONIS-DMRP.

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Site qualification/training:

Prior to study set-up, appropriate training will be given to the investigational staff.

Sites and data monitoring:

A remote review of eCRF for each study site will be performed by [REDACTED] according to the ONIS-DMRP.

A Site Initiation Visit (SIV) for all the participating sites will be carried out remotely by the study Clinical Research Associate (CRA) from [REDACTED]. Each SIV will be conducted prior to site activation to confirm preparedness for protocol execution, clarify the applicable regulations and requirements of the protocol and carefully review the process of implementing the protocol at the site. After that review, a remote call could be performed by [REDACTED] to the site to assist the principal investigator with queries management and to solve possible issues.

During study period two quality review meetings will be performed to review the study eCRF and to detect possible data discrepancies.

No on-site visit is expected for this study because no source data verification is planned, but, if an issue is identified in a site, it could be decided to perform a face-to-face visit to a site prior agreement between BI and [REDACTED]. For the sites close-out, [REDACTED] will inform the site investigator and site local EC by email about the site close-out, once all the data extraction and validation activities have been performed.

To enable evaluations, audits, or inspections from regulatory authorities or BI, the site investigator will be responsible for ensuring the accuracy and completeness of the data entered into the eCRF and for storing all relevant study documents, according to local regulations.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The use of secondary data extracted from EMR implies potential limitations, based on that these data were collected in an unstandardized fashion (not guided by a study protocol), but rather followed standard critical practice. However, in this study, most of the data collection will be registered in electronic forms in a structured fashion among study centres.

Specifically, the potential limitations in this study are:

- Misclassification bias: It occurs when a participant is categorized incorrectly. The diagnosis of patients with IPF and other PPF, might have been made following different methods and criteria among study centres and clinicians. This is particularly likely in the case of PPF (other than IPF), a term that has been recently introduced in medicine. In addition, the definition of cases with nintedanib-related diarrhoea might be subjected to bias (diarrhoea could be due to another reason). However, we reduced the risk of this bias by including only first cases of diarrhoea after nintedanib initiation.
- Sampling bias: As with most clinical diagnosis, it is possible that patients with less severe diarrhoea symptoms are misdiagnosed and incorrectly classified as non-diarrhoea cases. In addition, the classification of a diarrhoea episode as “first”, is based on self-reported information, which might be subjected to recall bias.

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- **Confounding:** Confounding is a type of bias in which the confounding variable is associated with the exposure and outcome variables. In this study, the objective is descriptive, and no cause-effect associations or modelling that can be influenced by confounding will be established. In this line, no control for confounding was established (e.g., adjusting models by cofounders, or matching of participants).
- **Missing data:** Since the data collection will be made in the framework of standard clinical care, data entry completeness cannot be assured. Thus, missing information will be extensively described and will be considered during results interpretation.
- **Generalization:** Since this is a national study, extrapolation of results to other countries should be taken with caution. Based on the inclusion of consecutive patients across multiple regions, it is expected that the results from this study will be representative of the Spanish population with IPF and other PPFs treated with nintedanib and may be generalizable to other regions with similar demographics and health care systems.
- **The reporting of diarrhoea indicators, nintedanib pattern of use, and diarrhoea management by the patient may be subjected by recall bias.** Also, the information to be collected by patient in the diary may not be complete or accurate. Patient may forget some information or commit some mistakes when filling it. However, the use of a patients' diary as a support document and the information provided by the EMR would be used to decrease this bias.
- **Information bias:** The baseline visit date should be as close as possible to the index date. However, many patients are unable to attend the hospital due to limitations caused by their condition itself. Therefore, the maximum period from the index date to the baseline visit has been extended from 5 days to 4 weeks to facilitate patient recruitment. This delay between the onset of the first diarrhoea episode and the date on which the information is collected may produce an information bias since the patient may not remember in detail the data necessary for the study.
- **The presence or not of diarrhoea and its evolution may be related to adherence to treatment with nintedanib or to other factors (e.g., having preventive diarrhoea treatment), but these variables will not be collected since it is not an objective of the study.**

9.10 OTHER ASPECTS**9.10.1 Data quality assurance**

A quality assurance audit/ inspection of this study may be conducted by the sponsor or sponsor's designees or by Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.10.2 Study records

Patients' data will be extracted from the source documents and entered in the eCRF, while newly collected data during study visits will be registered in the EMR and then entered in the eCRF. The EMR contains demographic, medical, treatment, and diagnostic information.

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The eCRF of each patient will be provided by [REDACTED] to the sites via remote data capture, according to the procedures described in the study DMRP.

9.10.2.1 Source documents

Source documents provide evidence of the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs will be transcribed from source documents by the investigator team and will match the data in the patient medical charts. The investigator will need previous and current medical records of the included patients in the study.

For eCRFs, **all** data must be derived from source documents.

9.10.2.2 Direct access to source data and documents

The investigator/ institution will permit study-related monitoring, audits, IEC reviews, and regulatory inspections providing direct access to all related source data/ documents. eCRFs and all source documents, including progress notes and copies of laboratory and medical test results, must be always available for review by the sponsor's clinical study monitor, auditor, and inspection by health authorities (e.g., Spanish Health Authorities, US Food and Drug Administration (FDA)).

9.10.3 Completion of study

Completion of study will be defined as the date in which the eCRFs in all sites are completed, queries are solved, and the ISF of each centre is updated and closed.

The completion of the study will be communicated to the involved EC and Spanish autonomous communities, according to Spanish Royal Decree 957/2020 of November 3 of the Ministry of Health and Social Policy (32).

9.10.4 Protocol deviations

All Protocol Deviations (PD) will be registered in the study Issue Log. Full details about the protocol deviation definition, classification, recording and general management, as well as about the Important PDs (iPD) of this study are documented in a separate ONIS-DMRP.

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10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out by [REDACTED] in compliance with the protocol, the European Regulation and Organic Law 3/2018 of 5 December on the Protection of Personal Data and the guarantee of digital rights and according to Spanish Royal Decree 957/2020 of November 3 of the Ministry of Health and Social Policy which publishes the guidelines on observational post-authorization studies for medicinal products for human use, and the local laws and regulations (32), the principles laid down in the Declaration of Helsinki, Guidelines for GPP, and the applicable BI and [REDACTED] SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and of any serious breaches of the protocol.

Insurance Cover: As a non-interventional study and according to the national and local regulations, an insurance policy is not applicable.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This ONIS will be initiated only after all required legal documentation has been reviewed and approved according to Spanish regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the study, informed consent must be obtained from each patient (or the patient's legally accepted representative) per GPP and according to the regulatory and legal requirements of Spain. If the patient has a face-to-face visit, a paper ICF will be signed and dated by the patient and by the investigator. A copy of the ICF will be provided to the subject and the original signed consent document will be retained in the study records, by the study investigator (i.e., pulmonologist), in a safe place. More information is provided in section **9.2.2 Study population**.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, the IEC, and by the regulatory authorities (i.e., the CA).

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11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS**11.1 DEFINITIONS OF ADVERSE EVENTS****Adverse Event**

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g., 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.

Adverse Drug Reaction

An ADR is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse, and medication errors.

Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any AE which

- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest

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

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases, and relevant history.

Arguments that may suggest a **reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug.
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced.
- **No medically sound alternative aetiologies** that could explain the event (e.g., pre-existing or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g., Stevens-Johnson syndrome).
- An indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g., pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g., after 5 half-lives).
Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).

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- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

- Mild: Awareness of sign(s) or symptom(s) which is / are easily tolerated.
Moderate: Enough discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

Pregnancy

In rare cases, pregnancy might occur in a ONIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The Investigator Site File (ISF) will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying serious ADR, only the Pregnancy Monitoring Form and not the ONIS AE form is to be completed. If there is a serious ADR associated with the pregnancy, an electronic ONIS AE form must be completed in addition.

The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason, the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the electronic ONIS AE form section/page in the (e)CRF from the time of providing oral or written consent to participate in the study (**see section 9.2.2**) onwards, until the end of the study:

- all ADRs (serious and non-serious) associated with nintedanib *
- all AEs with fatal outcome associated with nintedanib

All ADRs including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

Expedited Reporting of AEs and Drug Exposure during Pregnancy to BI Patient Safety and Pharmacovigilance

The following must be reported by the investigator on the electronic ONIS AE form and/ or Pregnancy Monitoring Form from the time of providing oral or writing consent to participate in the study onwards, until the end of the study, and provide BI unique entry point:

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Type of Report	Timeline
All serious ADRs associated with nintedanib *.	Immediately within 24 hours
All AEs with fatal outcome in patients exposed to nintedanib.	Immediately within 24 hours
All non-serious ADRs associated with nintedanib.*.	7 calendar days
Drug exposure during pregnancy	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and send the electronic ONIS AE form.

Information required

For each reportable AE, the investigator should provide the information requested on the electronic ONIS AE form. The electronic ONIS AE form will be a section of the eCRF that will contain the same required information and fields as the paper ONIS AE form. This page of the electronic ONIS AE Form will have a ‘button’ for saving the information. When this ‘button’ is clicked, automatically the eAE form (with all filled in information) will be notified to the email of local PV. In this way, each event (and each modification/update to any already reported event) will be notified immediately to PV once introduced in the eCRF.

The electronic ONIS AE form page in the eCRF will show a message for the investigator/delegate making them aware of the submission of the form to local PV when clicking the ‘button’.

In addition, eCRF will include email alerts to BI ONIS Lead or delegate to ensure proper PV oversight.

Should the EDC system not be available for more than 24 hours, reporting must occur via the paper ONIS AE form to the sponsor’s unique entry point. A copy of the paper form will be available in the ISF.

*The following consideration will be applied in this study:

Having a diarrhoea event is required as an inclusion criterion. For this reason, the first diarrhoea episode after nintedanib initiation which triggers the inclusion of the patient in the study will not be collected as an ADR in the electronic ONIS AE form.

During the study, the adverse reaction diarrhoea will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria:

CTCAE Grades Definitions	CTCAE Grades Term Diarrhoea
Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline.

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Grade 2: Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL.
Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.	Increase of ≥ 7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL.
Grade 4: Life-threatening consequences; urgent intervention indicated.	Life-threatening consequences: urgent intervention indicated.
Grade 5: Death related to AE.	Death.

Abbreviation: ADL= Activities of Daily Living

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing, and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse Event reporting to regulatory agencies will be done by the Marketing Authorisation Holder (MAH) according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor regarding publication of the study results are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

Study results will be submitted for publication in national and/ or international peer-reviewed scientific journal and to scientific conferences or congresses.

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14. APPENDIX

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Date	Title
1	30 Oct 2023	Signed ENCePP Checklist for Study Protocols
2	Document in progress	List of all participating sites and investigators
3	25 Apr 2024	Data Management and Review Plan
4	29 Oct 2024	Patient Information Sheet /Inform consent form
5	8 Apr 2024	Patient diary
6	24 Apr 2024	Case Report Form
7	19 Sep 2024	Statistical and Epidemiological Analysis Plan
8	14 Nov 2023	Investigator data collection supporting guide (Guía de soporte al investigador para la recogida de datos)
9	See Annex 4	Signed Coordinating Investigator Signature Page

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Observational, multicentre, prospective, real-world post-authorization safety study describing the achievement of nintedanib-associated DIArrhoea control after 12 weeks of follow-up in patients with idiopathic puLmonary FIBrosis (IPF) and progressive pulmonary fibrosis (other than IPF) in Spain: the DIALFIB study

EU PAS Register® number: EUPAS106524
Study reference number (if applicable): 1199-0545

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4,6
1.1.2 End of data collection ²	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4,6
1.1.3 Progress report(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.4 Interim report(s)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
1.1.5 Registration in the EU PAS Register®	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4,6

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¹ Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
² Date from which the analytical dataset is completely available.

Comments:

1.1.1 We report dates for First Patient In (start of data collection)..

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

2.1.1 No, because this information is in the Rationale and Background section (section n°7).2.1.4 and 2.1.5: No, since all primary and secondary objectives are merely descriptive.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11

Comments:

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<u>Section 4: Source and study populations</u>	Yes	No	N/A	Section Number
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2; 4,6
4.2.2 Age and sex	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2
4.2.3 Country of origin	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.2.4 Disease/indication	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2
4.2.5 Duration of follow-up	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.2

Comments:

4.2.3: No, since we will include all patients treated in Spanish hospitals, regardless of their country of origin.

<u>Section 5: Exposure definition and measurement</u>	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.3 Is exposure categorised according to time windows?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.6 Is (are) (an) appropriate comparator(s) identified?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

All primary and secondary objectives are purely descriptive, and no exposure was included.

<u>Section 6: Outcome definition and measurement</u>	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.2

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<u>Section 6: Outcome definition and measurement</u>	Yes	No	N/A	Section Number
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.3; 9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYs, health care services utilisation, burden of disease or treatment, compliance, disease management)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

6.3: Not applicable but the references used to define the terms used in the outcomes and/or to studies including/validating these outcomes are provided (section 9.3.2).

<u>Section 7: Bias</u>	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9

Comments:

7.1 Not applicable since we only include patients who are treated with nintedanib.
7.2 Not applicable we do not randomize patients.

<u>Section 8: Effect measure modification</u>	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.1

Comments:

<u>Section 9: Data sources</u>	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

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<u>Section 9: Data sources</u>	Yes	No	N/A	Section Number
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1; 9.2.3; 9.4
9.1.3 Covariates and other characteristics?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1;9.2.3; 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.3; 9.4; 9.10.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.3; 9.4; 9.10.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.3.3 Covariates and other characteristics?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

9.3 No, since they will be described in the Statistical and Epidemiological Analysis Plan (SEAP).

9.4 No linkage method will be used.

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.2 Is study size and/or statistical precision estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5
10.3 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.4 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.5 Does the plan describe methods for analytic control of confounding?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

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<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.7 Does the plan describe methods for handling missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9
10.8 Are relevant sensitivity analyses described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7

Comments:

Sensitivity and further analysis will be specified in the SEAP.

<u>Section 11: Data management and quality control</u>	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.8;9.10.1
11.3 Is there a system in place for independent review of study results?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6

Comments:

<u>Section 12: Limitations</u>	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias? 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	<input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/>	<input checked="" type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/>	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.1;9.2.2; 9.5

Comments:

<u>Section 13: Ethical/data protection issues</u>	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10

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Comments:

13.1: The specific requirements of EC are not described in protocol but in Section 10.1 is explained that the study will be initiated only after all required legal documentation has been reviewed and approved according to Spanish regulations.

<u>Section 14: Amendments and deviations</u>	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5; 9.10.4

Comments:

<u>Section 15: Plans for communication of study results</u>	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12

Comments:

Name of the main author of the protocol: [REDACTED]

Date: dd/Month/year

Signature: _____

ENCEPP checklist signed by the main protocol author is available as a stand-alone document ([see Annex 1](#)).

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**ANNEX 3. MANAGE SITE AND PHYSICIAN / INVESTIGATOR
SELECTION, CONTRACTING, AND TRAINING**

See section 9.2.1.1

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ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

As this is a “high risk” PASS study, Boehringer approvers signatures are collected in DMS for submission documents.

The Coordinating Investigator signature is provided via validated DocuSign, as a stand-alone document (see [Annex 1](#)).

Study Title: Observational, multicentre, prospective, real-world post-authorization safety study describing the achievement of nintedanib-associated **DI**Arrhoea control after 12 weeks of follow-up in patients with idiopathic pu**L**monary **FIB**rosis (IPF) and progressive pulmonary fibrosis (other than IPF) in Spain: the DIALFIB study

Study Number: 1199-0545

Protocol Version and date: Version 3, 29 October 2024

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.

Coordinating Investigator: 

Signature:

BOEHRINGER INGELHEIM Group of Companies

ONIS New Data Collection Protocol

Study number: 1199-0545

Document number: c45099814-01

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11 Nov 2024. ONIS lead associate note: As said before, this is a “high risk” PASS study and Boehringer approvers’ signatures should be collected in DMS for submission documents.

Recently, there has been a massive data migration from DMS for submission documents to the new platform OMP. Some approvers are pending to receive access to this new platform, and they still cannot sign.

After discussing the situation with the ONIS lead, and to be agile enough to avoid an undesirable delay, in this exceptional scenario, Boehringer approvers will sign the protocol using validated DocuSign. This does not affect the subject’s safety or the data integrity.

Study Number: 1199-0545

Protocol Version and date: Version 3, 29 October 2024

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.

ONIS lead: [Redacted]

Signed by: [Redacted]
[Redacted]
Signer Name: [Redacted]
Signing Reason: I approve this document
Signing Time: 11-Nov-2024 | 11:32:44 AM CET
[Redacted]

ONIS Lead Line Manager: [Redacted]

Firmado por: [Redacted]
[Redacted]
Nombre del firmante: [Redacted]
Motivo de la firma: Apruebo este documento
Hora de firma: 11-nov.-2024 | 12:12:59 PM CET
[Redacted]

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ONIS New Data Collection Protocol

Study number: 1199-0545

Document number: c45099814-01

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Global TM Epi: [redacted]

Signed by: [redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 11-Nov-2024 | 1:55:26 PM CET
[redacted]

Global Medical Advisor: [redacted]

Signed by: [redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 12-Nov-2024 | 3:44:40 PM CET
[redacted]

EU-QPPV: [redacted]

Signed by: [redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 11-Nov-2024 | 11:59:34 AM CET
[redacted]

Statistician: [redacted]

Signed by: [redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 12-Nov-2024 | 2:55:31 PM CET
[redacted]

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ONIS New Data Collection Protocol

Study number: 1199-0545

Document number: c45099814-01

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ABRT Chair: [Redacted]

Signed by: [Redacted]
[Redacted]
Signer Name: [Redacted]
Signing Reason: I approve this document
Signing Time: 13-Nov-2024 | 8:40:10 AM CET
[Redacted]

Certificate Of Completion

Envelope Id: 7944E203C3DB437AACA613A1BA05C468

Status: Completed

Subject: Complete with Docusign: DIALFIB protocol-v3.0-29oct2024-Due date November 13th

Source Envelope:

Document Pages: 65

Certificate Pages: 5

AutoNav: Enabled

Envelopeld Stamping: Enabled

Time Zone: (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna

Signatures: 7

Initials: 0

Envelope Originator:

IP Address:

Record Tracking

Status: Original

Holder:

Location: DocuSign

11/11/2024 11:17:42 AM

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Electronic Record and Signature Disclosure:

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Signer Events	Signature	Timestamp
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[REDACTED] GEpi
Boehringer Ingelheim Validated Production
Security Level: Email, Account Authentication
(Required)

[REDACTED]

Signature Adoption: Pre-selected Style
Signature ID:
[REDACTED]
Using IP Address: [REDACTED]

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Signed: 11/11/2024 1:55:32 PM

With Signing Authentication via DocuSign password
With Signing Reasons (on each tab):
I approve this document

Electronic Record and Signature Disclosure:
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Editor Delivery Events	Status	Timestamp
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Agent Delivery Events	Status	Timestamp
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Intermediary Delivery Events	Status	Timestamp
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Certified Delivery Events	Status	Timestamp
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Carbon Copy Events	Status	Timestamp
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Witness Events	Signature	Timestamp
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Notary Events	Signature	Timestamp
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Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	11/11/2024 1:54:31 PM
Signing Complete	Security Checked	11/11/2024 1:55:32 PM
Completed	Security Checked	11/13/2024 8:40:18 AM

Payment Events	Status	Timestamps
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Electronic Record and Signature Disclosure
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Parties agreed to:

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available to me by the Company during the course of the business relationship with you.