Boehringer Ingelheim

Protocol for non-interventional studies based on existing data

Document Number:	c17367432-01
BI Study Number:	1199-0295
BI Investigational Product(s):	Nintedanib (OFEV®)
Title:	A multicentre, retrospective chart review study to describe the clinical profile of idiopathic pulmonary fibrosis (IPF) patients treated with nintedanib (OFEV®) in real-world practice in Spain.
Protocol version identifier:	1.0
Date of last version of protocol:	11 May 2017
PASS:	No
EU PAS register number:	Not yet available (study will be registered in EU PAS Register (ENCePP) and clinicaltrials.gov)
Active substance:	Anatomical main group: L - Antineoplastic and immunomodulating agents Therapeutic subgroup: L01 - Antineoplastic agents Pharmacological subgroup: L01X - Other antineoplastic agents Chemical subgroup: L01XE - Protein kinase inhibitors Chemical substance: L01XE31 - Nintedanib
Medicinal product:	Nintedanib
Product reference:	EU/1/14/979
Procedure number:	EMEA/H/C/003821
Joint PASS:	No
Research question and objectives:	The present study has been designed to characterize IPF patients treated with nintedanib (OFEV®), at time of treatment initiation, with respect to their clinical profile based on real-world data from January 2016 in Spanish Pulmonology Services. The primary objective of the study is to describe the distribution of patients across different lung function categories (%FVC and DLCO serving as surrogate markers for IPF severity) of IPF patients at the time of treatment initiation with nintedanib (OFEV®) in routine clinical practice. The secondary objectives are:

	- To describe demographic and clinical baseline characteristics of IPF patients at time of treatment initiation with nintedanib (OFEV®) - To describe comorbidity prevalence at time of treatment initiation - To describe the distribution of patients across different lung function categories based on reimbursement threshold (FVC >80%, 50-80%, and <50%)
Country(-ies) of study:	Spain
Author:	(Trial Clinical Monitor) Mobile:
Marketing authorisation holder(s):	MAH: Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein This study is initiated, managed and sponsored by:
EU-QPPV:	Not applicable
Signature of EU-QPPV:	Not applicable
Date:	11 May 2017

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

6MWT	6 Minutes Walking Test
!"#$%	!&'()*+ ",-+./0+ 1' #'1*)+2'(3/, 4 $5/16)3/, %+(*3+5*/,
78	7/'95*(&'5 8(&'09'*2
:!	:/2-'3'(3 !639/5*34
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
DILD	Diffuse Interstitial Lung Disease
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
DMP	Data Management Plan
EDC	Electronic Data Capture
"; <=$$>	"65/-'+(=6+0*?*'1 $'5,/(?/5 $9+52+)/@*&*0+()'
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
A$> :B:	A0/C+0 $9+52+)/@*&*0+()' :0*(*)+0 B5*+0 ://51*(+3/5
HRCT	High-resolution Chest Tomography
IEC	Independent Ethics Committee
IPF	Interstitial Pulmonary Fibrosis
D:E	:+5C/(#/(/F*1' B5+(,?'5 :/'??*)*'(3
G$>#	G/)+0 $9+52+)/@*&*0+()#+(+&'5
#!H	#+5I'3*(& !639/5*J+3*/(H/01'5
2#K:	#/1*?*'1 #'1*)+0 K',+5)9 :/6()*0
L8%	L/(<8(3'5@'(3*/(+0%3614
%!$	%3+3*,3*)(+004,*, $0+(
%M	%3+(1+5M'@*+3*/(
%2$:	%622+54 /? $5/16)3 :9+5+)3'5*,3*),
%E$	%3+(1+5E-'5+3*(&$5/)'165'
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BD8	B45/,*(' I*(+,' *(9*C*3/5
;8$	;,6+0 8(3'5,3*3*+0 $('62/(*+

3. RESPONSIBLE PARTIES

Team Member Medical Affairs		
Medical Advisor		
Medical		
Trial Clinical Monitor		
Coordinator Investigator		
Coordinator Investigator		

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: OFEV®			
Name of active ingredient: Nintedanib			
Protocol date: 11 May 2017	**Study number:** 1199-0295	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
Title of study:	A multicentre, retrospective chart review study to describe the clinical profile of idiopathic pulmonary fibrosis (IPF) patients treated with nintedanib (OFEV®) in real-world practice in Spain.		
Rationale and background:	Nintedanib (OFEV®) is a small molecule tyrosine kinase inhibitor (TKI) that targets growth factor receptors, which have been shown to be involved in the mechanisms by which pulmonary fibrosis occurs. Nintedanib (OFEV®) has been reimbursed for IPF in Spain on December 2015. There is no available data on its use in routine clinical practice after its marketing authorization.		
Research question and objectives:	The present study has been designed to characterize IPF patients treated with nintedanib (OFEV®) with respect to their clinical profile based on real-world data from January 2016 in Spanish Pulmonology Services. The **primary objective** of the study is to describe the distribution of patients across different lung function categories (%FVC and DLCO serving as surrogate markers for IPF severity) of IPF patients treated with nintedanib (OFEV®) in routine clinical practice, at the time of treatment initiation. As no established severity grading exists, the stratification published by Nathan et al. [9] based on pulmonary function impairment and survival differences will be applied in the study. Patients will be classified with regards to the FVC and DLCO serving as surrogates for severity: FVC: - Mild IPF: FVC > 70% predicted - Moderate IPF: FVC 50% to 70% predicted (*) - Severe IPF: FVC < 50% predicted (*) %FVC has been adapted from 55 to 50% to be aligned with nintedanib (OFEV®) clinical trials program. DLCO: - Mild IPF: DLCO >50% predicted - Moderate IPF: DLCO 35% to 50% predicted		

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Name of active ingredient: Nintedanib			
Protocol date: 11 May 2017	**Study number:** 1199-0295	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
	- Severe IPF: DLCO <35% predicted The **secondary objectives** are: o To describe demographic and clinical baseline characteristics of IPF patients at time of treatment initiation with nintedanib (OFEV®) o To describe comorbidity prevalence at time of treatment initiation o To describe the distribution of patients across different lung function categories based on reimbursement threshold (FVC>80%, 50-80%, and <50%)		
Study design:	Non-interventional study based on medical charts of multiple centers, of IPF patients treated with nintedanib (OFEV®). Patients will be characterized at time of treatment initiation (cross-sectional design). IPF patients with a confirmed diagnosis of IPF, who initiated treatment with nintedanib from 01 January 2016, will be selected.		
Population:	Approximately 35 Pulmonology Services of Hospitals in Spain will be the basis for the study. The sites will be distributed across whole Spain and will be selected according to previous experience in clinical trials, named-patient program and access to nintedanib (OFEV®). The participating investigators will review all medical records of their IPF patient's since 01 January 2016 and select all patients who initiated treatment with nintedanib (OFEV®) in the study period.		
Variables:	All variables will be obtained from medical records: - IPF diagnosis: method of diagnosis, date of diagnosis, , UIP pattern - At nintedanib (OFEV®) initiation: - OFEV® treatment initiation date and dose - Patient demographics (age, sex, race) - Physical examination (height, weight, BMI, 6 minutes walking test (6MWT)) - Smoking status - Breathlessness grade - Pulmonary function: %FVC, %DLCO - Comorbidities - Concomitant medication - Previous IPF treatment with pirfenidone, if any: initiation date,		

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	end date - Number of exacerbations due to IPF in the previous year
Data sources:	Data will be collected by the Investigator from patient medical records and will be entered to an electronic case report form (eCRF) which will include all the study variables.
Study size:	For calculating the sample size, variables on the patient's lung function (FVC, DLCO) will be dichotomized. The following table illustrates the precision of estimates of the prevalence of a specific lung function profile within the population of interest depending on the observed rate of affected patients and the sample size. The dropout rate is assumed to be 10% for all scenarios. Precision is estimated based on two-sided 95% confidence intervals. Precision table:

N	N to be analyzed	% observed in subsample	95% CI	Precision
100	90	7.8% (7 out of 90)	[2.2; 13.3]	±5.6
150	135	8.1% (11 out of 135)	[3.5; 12.8]	±4.7
175	158	8.2% (13 out of 158)	[3.9;12.5]	±4.3
100	90	50.0% (45 out of 90)	[39.7; 60.3]	±11.3
150	135	50.4% (68 out of 135)	[41.9; 58.8]	±8.5
175	158	50.0% (79 out of 158)	[42.2;57.8]	±7.8

It can be seen that by raising the sample size from 100 to 150 patients, precision improves to less than ±5% for the small proportion of 8% and to less than 10% for the large sample of 50%. Precision can be

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	further improved to less than ±4.5% for the small sample of 8% and to less than 8% for the large sample of 50% if 175 patients will be recruited. Planning a recruitment of 175 patients allows for an acceptable precision of prevalence of a specific lung function profile estimates.		
Data analysis:	Since the study is essentially descriptive the variables included in the study objectives will be analysed with measures of central tendency (mean and median), variability/dispersion (standard deviation and interquartile ranges), absolute and relative frequencies, and ranges. 95% confidence intervals will be provided as appropriate.		
Milestones:	Planned final protocol: May 2017 Planned start of data collection: September 2017 Planned end of data collection: December 2017 Planned final study report: March 2018		

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Start of data collection	01 September 2017
End of data collection	30 December 2017
Registration in the EU PAS register	May 2017
Final report of study results:	March 2018

7. RATIONALE AND BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is one of the most frequent forms of diffuse interstitial lung diseases (DILD). It is defined as a limited chronic fibrosing lung interstitial pneumonia of unknown cause associated with radiological or pathological pattern of usual interstitial pneumonia (UIP). Pathogenically, it is characterized by epithelial damage with fibroblast-myofibroblast accumulation in the alveolar spaces; repeated injury of epithelial cells leads to an abnormal repair, an uncontrolled proliferation of fibroblasts, and differentiation thereof into myofibroblasts and excessive extracellular matrix deposition in the interstitial space [1]. Affected patients usually show common clinical features, such as dry cough and dyspnea; the disease usually appears as a restrictive ventilatory defect with decreased gas transfer capacity.

IPF usually affects people over 50 years of age. Various studies have been conducted to evaluate the incidence and prevalence of IPF. The most reliable data estimate that in European countries, IPF prevalence ranged from 1.25 per 100,000 population in Belgium to 23.4 per 100,000 population in Norway. The annual IPF incidence ranged from 0.22 per 100,000 population in Belgium to 7.94 per 100,000 population in the UK [2]. Based on this data, it is believed that, in Spain, IPF could be affecting around 7500 people[3]. Although the natural history of IPF is highly variable, the disease is associated with a poor prognosis, and the median survival is around three years [4].

The first international consensus on the diagnosis and treatment of IPF was published in 2000. This consensus recognized that the histological pattern of UIP is the one that identifies IPF. Moreover, in this consensus it was included a group of functional criteria defining disease stabilization or progression, very useful when monitoring treatment response in every single patient. A new consensus in 2011 [5] (updated on treatment recommendations in 2015 [6]) has better established diagnostic criteria according to the findings on high-resolution chest tomography (HRCT) and lung biopsy and it has established new therapeutic recommendations[5]. The updated recommendations included a conditional recommendation for use of the new agents (pirfenidone and nintedanib), and also for the use of antiacids drugs.

Nintedanib (OFEV®) is a small molecule tyrosine kinase inhibitor (TKI), targets growth factor receptors, which have been shown to be involved in the mechanisms by which pulmonary fibrosis occurs. Most importantly, nintedanib (OFEV®) inhibits platelet-derived growth factor receptor, fibroblast growth factor receptor and vascular endothelial growth factor receptor [7].

The clinical efficacy of nintedanib (OFEV®) was studied in patients with IPF in two trials with identical design phase III, randomized, double-blind, placebo-controlled (INPULSIS-1 [8] and INPULSIS-2[7]). Patients with baseline FVC predicted less than 50% or a factor of transfer of carbon monoxide (DLCO, corrected for haemoglobin) provided below 30% at

baseline were excluded from the trials. Patients were randomized in a ratio 3:2 to nintedanib (OFEV®) treatment with 150 mg or placebo treatment twice daily for 52 weeks. The primary endpoint was the annual loss of FVC. In the INPULSIS-1 trial significant differences were achieved in the primary endpoint, between the placebo group (204 patients) and the nintedanib (OFEV®) group (309 patients), the mean±SD loss of FVC observed was-239.9±18.71 in placebo group and -114.7±15.3 in the nintedanib (OFEV®) group (p<0.0001). In the INPULSIS-2 trial significant differences were achieved in the primary endpoint, between the placebo group (219 patients) and the nintedanib (OFEV®) group (329 patients), the mean±SD loss of FVC observed was -207,3±19.31 in placebo group and -113.6±15.73 in the nintedanib group (p<0.0001). These results led to its approval on the 15th of January 2015 by the European Commission for the treatment of IPF in adults.

On June 2014 a named-patient use (NPU) program of nintedanib started in Spain offering the treatment to the same type of patients than in clinical trials (%FVC>50). Afterwards, on September 2014, pirfenidone was available on the market in Spain, for IPF patients with FVC between 50-80%. Therefore, nintedanib NPU program was limited to patients not responding to pirfenidone, or when pirfenidone was not reimbursed (FVC >80%), or with emphysema and/or not clear IUP pattern. On 15 January 2015, nintedanib (OFEV®) obtained the EU approval for all IPF patients and NPU program in Spain was also offered to all patients independent of their %FVC. On December 2015, OFEV® was finally available with reimbursement in Spain and nintedanib NPU program ended. Compared to pirfenidone, nintedanib reimbursement is not restricted based on FVC% predicted level.

There is no available data on nintedanib use in routine clinical practice. For this reason, this retrospective chart review is proposed to characterize clinical profile of IPF patients treated with nintedanib (OFEV®) during routine clinical practice in Spain.

8. RESEARCH QUESTION AND OBJECTIVES

The present study has been designed to characterize IPF patients treated with nintedanib (OFEV®) with respect to their clinical profile based on real-world data from Spanish Pulmonology Services.

The primary objective of the study is to describe the distribution of patients across different lung function categories (%FVC and DLCO serving as surrogate markers for IPF severity) of IPF patients treated with nintedanib (OFEV®) in routine clinical practice, at the time of treatment initiation.
As no established severity grading exists, the stratification published by Nathan et al. [9] based on pulmonary function impairment and survival differences will be appli
ed in the study:
FVC:
- Mild IPF: FVC > 70% predicted
- Moderate IPF: FVC 50% to 70% predicted (*)
- Severe IPF: FVC < 50% predicted

(*) %FVC has been adapted from 55 to 50% to be aligned with nintedanib (OFEV®) clinical trials program.

DLCO:
- Mild IPF: DLCO >50% predicted
- Moderate IPF: DLCO 35% to 50% predicted
- Severe IPF: DLCO <35% predicted

The secondary objectives are:
1.- To describe demographic and clinical baseline characteristics of IPF patients at time of treatment initiation with nintedanib (OFEV®)
2.- To describe comorbidity prevalence at time of treatment initiation
3.- To describe the distribution of patients across different lung function categories based on reimbursement threshold (FVC >80%, 50-80%, and <50%)

9. RESEARCH METHODS

9.1 STUDY DESIGN

This non-interventional study, based on medical charts, will be conducted in approximately 35 Pulmonology Services of Hospitals in Spain. IPF patients will be characterized at time of nintedanib initiation (cross-sectional study design).

The participating investigators will review their IPF patient's medical records since 01 January 2016 up to the end of data collection date and identify all IPF patients who initiated nintedanib (OFEV®) during that time. To minimize selection bias, a simple randomization will be applied. The Investigator will share an anonymized list of all of patients who meet selection criteria with the CRO. The list will include the minimum patient data to be identifiable by the investigator, for example, age, gender and treatment initiation date. Then, CRO will generate a random sequence of the 5 patients to be included and will inform the Investigator.

As this is a non-interventional study, designed to reflect real-world clinical practice, the decision to start treatment with OFEV® is prior to and independent of the selection of the patient in the study and based on routine clinical practice and medical judgment criteria. In addition, no intervention, either diagnostic or therapeutic, will be applied to patients other than that used for routine clinical practice.

9.2 SETTING

Approximately 35 Pulmonology Services of Hospitals in Spain will be the source of data collection. Sites will be selected according to previous experience in clinical trials, NPU program, and access to nintedanib (OFEV®).

9.3 VARIABLES

The following variables will be obtained from the patient medical records:

- IPF diagnosis: method of diagnosis, date of diagnosis, , UIP pattern (according to international guideline, Raghu et al. 2011)
- At nintedanib (OFEV®) initiation:
  - OFEV® treatment initiation date and dose
  - Patient demographics (age, sex, race)
  - Physical examination (height, weight, BMI, 6 minutes walking test (6MWT))
  - Smoking status (current smokers, former smokers and never smokers)
  - Breathlessness grade mMRC [10]
  - Pulmonary function: %FVC, %DLCO
  - Concomitant medication (active substance, dose, initiation date, indication)
  - Previous IPF treatment with pirfenidone, if any: dose, initiation date, end date
  - Number of exacerbations due to IPF in the previous year

- Comorbidities (Pulmonary infection, Emphysema (combined pulmonary fibrosis and emphysema), Pulmonary hypertension, Lung cancer, Gastroesophageal reflux, Cardiovascular diseases, Hypertension, Dyslipidemia, Diabetes mellitus, Obstructive sleep apnoea, Other)

9.3.1 Exposures

Patients in this study will have been prescribed nintedanib (OFEV®) treatment for their IPF on or after 01 January 2016. Prescription of the treatment will have been done under the sole responsibility of the healthcare professional. The date of treatment initiation and the dose will be assessed.

In Spain, nintedanib (OFEV®) is on the market since December 2015, however, in some regions of the country, nintedanib is only reimbursed in a limited type of IPF patients (for example, with a %FVC between 50% and 80% or just >50%), although the indication of local label include all type of IPF patients, independent of their pulmonary function.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcome of the study is the distribution of patients across different lung function categories (%FVC and DLCO serving as surrogate markers for IPF severity) of IPF patients at the time of treatment initiation with nintedanib (OFEV®) in routine clinical practice.

As no established severity grading exists, the stratification published by Nathan et al. [9] based on pulmonary function impairment and survival differences will be applied.

Patients will be classified with regards to the FVC and DLCO serving as surrogates for severity:

FVC:
- Mild IPF: FVC > 70% predicted
- Moderate IPF: FVC 50% to 70% predicted (*)
- Severe IPF: FVC < 50 % predicted

(*) %FVC has been adapted from 55 to 50% to be aligned with nintedanib (OFEV®) clinical trials program.

DLCO:
- Mild IPF: DLCO >50% predicted
- Moderate IPF: DLCO 35% to 50% predicted
- Severe IPF: DLCO <35% predicted

The study outcomes are defined as follows:

- FVC is the total amount of air exhaled during the lung function test % predicted).
- DLCO is the extent to which oxygen passes from the air sacs of the lungs into the blood (% predicted).

9.3.2.2 Secondary outcomes

To describe demographic and clinical baseline characteristics of IPF patients at time of treatment initiation with nintedanib (OFEV®).
Descriptive statistics will be provided for the following variables:

- IPF diagnosis: frequency of each method of diagnosis (SLB, HRCT), mean duration of the disease from diagnosis to treatment initiation, frequency of patients with associated emphysema, frequency of patients with UIP pattern (according to international guideline, Raghu et al. 2011)
- At nintedanib (OFEV®) initiation:
  - OFEV® treatment initiation date and frequency of each dose
  - Patient demographics (age, male and female, race)
  - Physical examination (height, weight, BMI, mean distance of the 6 minutes walking test (6MWT))
  - smoking status (current smokers, former smokers and never smokers)
  - breathlessness grade mMRC [10]
  - concomitant medication (active substance, dose, initiation date, indication)
  - Mean Number and frequency of exacerbations due to IPF in the previous year

To describe comorbidity prevalence at time of treatment initiation: frequency of each comorbidity.

- Comorbidities (Pulmonary infection, Emphysema (combined pulmonary fibrosis and emphysema), Pulmonary hypertension, Lung cancer, Gastroesophageal reflux, Cardiovascular diseases, Hypertension, Dyslipidemia, Diabetes mellitus, Obstructive sleep apnoea, Other)

To describe the distribution of patients across different lung function categories based on reimbursement threshold (FVC >80%, 50-80%, and <50%)

9.3.3 Covariates

Not applicable

9.4 DATA SOURCES

Data collection will be limited to those available in the medical records of selected patients. All medical records of the 35 included centers will be screened for IPF patients and then patients who initiated treatment with nintedanib since 01 January 2016 up to the end of data collection date will be identified. 5 patients per site will be selected based on a simple randomization of all the patients from each physician.

Demographics and comorbidities will be obtained from the available information of patient's medical records on the date of treatment initiation.

Most of data will be available in the charts but as a routine clinical practice, some data could be missing. However, it will be recorded in the CRF if data for the respective variables was not available. Data will be included in an eCRF by investigators.

9.5 STUDY SIZE

The following table illustrates the precision of estimates of the prevalence of a specific lung function profile within the population of interest depending on the observed rate of affected patients and the sample size. The dropout rate is assumed to be 10% for all scenarios.

Precision is estimated based on two-sided 95% confidence intervals.

Table 1 Precision table

N	N to be analyzed	% observed in subsample	95% CI	Precision
100	90	7.8% (7 out of 90)	[2.2; 13.3]	±5.6
150	135	8.1% (11 out of 135)	[3.5; 12.8]	±4.7
175	158	8.2% (13 out of 158)	[3.9;12.5]	±4.3
100	90	50.0% (45 out of 90)	[39.7; 60.3]	±11.3
150	135	50.4% (68 out of 135)	[41.9; 58.8]	±8.5
175	158	50.0% (79 out of 158)	[42.2;57.8]	±7.8

It can be seen that by raising the sample size from 100 to 150 patients, precision improves to less than ±5% for the small sample of 8% and to less than 10% for the large sample of 50%. Precision can be further improved to less than ±4.5% for the small proportion of 8% and to less than 8% for the large sample of 50% if 175 patients will be recruited.

Planning a recruitment of 175 patients allows for an acceptable precision of prevalence of a specific lung function profile (see section 9.3.2.1) estimates.

9.6 DATA MANAGEMENT

The data will be entered by the investigators themselves and/or authorized personnel directly in the electronic case report form (eCRF). A Data Management Plan (DMP) will be prepared to describe all functions, processes, and specifications for data collection, cleaning and validation.

Data Management will be performed by the CRO . This contract organization will be responsible for the development and implementation of the data management plan and preparation of the data handling report according to the sponsor´s standards.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

Once the study has been completed and all data from the last patient have been recorded, the database will be closed and statistical analysis will be performed.

9.7 DATA ANALYSIS

The proposed methods for statistical analysis presented below are a summary of the methods that will be applied in the study to analyse the data collected and to answer the study objectives. Missing data will not be imputed in the main analysis (but eventually in sensitivity analyses as deemed appropriate). When applicable, the presence of potential outliers will be indicated. Analysis will primarily be performed including these outliers. However, excluding the respective patients in sensitivity analyses might be a reasonable approach to assess the impact of these outliers.
Analyses will be performed by the CRO . Since the study is essentially descriptive the variables included in the study objectives will be analysed with measures of central tendency (mean and median), variability/dispersion (standard deviation and

interquartile ranges), absolute and relative frequencies, and ranges. 95% confidence intervals will be provided as appropriate.

Missing values and data not available in the charts will be displayed in separate categories.

All the analyses will be performed using the Statistical Package for the Social Sciences (SPSS), version 22.

9.7.1 Main analysis

For the primary objective absolute and relative frequencies of patients across different lung function categories will be calculated.

For the secondary objectives:
To describe demographic and clinical baseline characteristics of IPF patients at time of treatment initiation with nintedanib (OFEV®) and prevalence of comorbidities, descriptive statistics and confidence interval at 95% will be calculated for the key variables defined. For the quantitative variables the number of evaluable patients and the measures of central tendency and dispersion (median, the standard deviation, the median, Q1 and Q3) will be obtained, and for the qualitative variables the absolute and relative frequencies relative to the total of patients and to the total of patients with data (total percentage and valid percentage, respectively) will be obtained.
For the secondary objective to describe the distribution of patients based on reimbursement threshold, absolute and relative frequencies of patients across different lung function categories will be calculated.

9.8 QUALITY CONTROL

To improve and secure data quality, automatic data checks upon data entry will be done within the eCRF. In the eCRF, plausible ranges of values for numeric data entries as well as logical data entries and listings will be provided for each entry field. Based on this, checks on completeness and plausibility will be performed upon data entry in the eCRF.

Validity of data entry thus is ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the document list or investigator. All corrections will be visible from the system audit trail.

No regular source data verification is planned in this study. However, in case of decreasing compliance (i.e. of missing data, data discrepancies, protocol violations, etc.) a for-cause audit or risk-based monitoring visit may be performed.

In addition, a quality assurance audit/inspection of 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 document (if applicable).

9.9 LIMITATIONS OF THE RESEARCH METHODS

A non-interventional study is the most suitable design to obtain information about the use of medicines in everyday therapeutic practice and thus for investigating questions regarding routine clinical practice.

The selection criteria are less restrictive than the ones of a randomized clinical trial, which will permit the enrolment of a broader patient population. The choice of nintedanib (OFEV®) therapy will have been done before the study initiation at the discretion of the investigator. However, as the study is limited to the hospital setting, patients treated in other clinical settings may not be part of the sample. In addition only patients initiating nintedanib (OFEV®) will be described and no information on IPF patients not initiating this treatment or on other treatments will be collected in this study. This has the limitation that it is not feasible to put the results into perspective to IPF patients initiating other kinds of treatments.

Another limitation is that data in medical records may have missing values and could reduce the validity of conclusions. However, the parameters collected in this study are those most frequently collected for IPF in real-world practice.

Precision of estimates could be improved with a higher sample size. However as it was stated in the sample size justification, provided an acceptable accuracy, and considering the scarce prevalence of the disease, it is a representative number of patients.

Finally, due to the cross-sectional study design no conclusion on any causal association could be drawn.

9.10 OTHER ASPECTS

The study will be initiated only after all required legal documentation has been reviewed and approved by the respective IEC and competent authority (CA) according to national and international regulations. The IEC/CA will be notified about the end of the study (last patient included) or early termination of the study.

9.11 SUBJECTS

Approximately 175 IPF patients from 35 Pulmonology Services in Spain are planned to be included in the study.

To be eligible to participate in the study, patients must meet the following selection criteria.

Inclusion criteria:

Patients could be included in the study if all of the following criteria are met:

1. The patient is at least 18 years old
2. The patient has IPF diagnosis according to most recent ATS/ERS/JRS/ALAT IPF guideline for diagnosis and management [5]
3. The patient newly initiated treatment with nintedanib (OFEV®) since 01 January 2016 up to end of data collection date, according to the approved local SmPC.

Exclusion criteria:

Patients will be excluded if the following criterion is met:

1. Patients treated with nintedanib within a clinical trial or named-patient program or with any prior treatment of nintedanib.

9.11.1 Withdrawal criteria

Not applicable. Retrospective chart review, with no direct contact to patients. See section 10.

9.12 BIAS

In order to ensure representativeness of patients among the whole country, each Investigator will include 5 patients. To minimize selection bias, a simple randomization will be applied. The Investigator will share an anonymized list of all of patients who meet selection criteria with the CRO. The list will include the minimum patient data to be identifiable by the investigator, for example, age, gender and treatment initiation date. Then, CRO will generate a random sequence of the 5 patients to be included and will inform the Investigator.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, current legislation in Spain concerning the conduct of observational studies (Orden SAS/3470/2009), relevant BI Standard Operating Procedures (SOPs) and following Good Epidemiological Practice Guideline (GEP) and the guideline for good pharmacoepidemiological practice (GPP).

The study will be initiated only after all required legal documentation has been reviewed and approved by the respective IEC and CA according to national regulations. The same applies for the implementation of changes introduced by protocol amendments.

Retrospective observational studies can be exempt from a written informed consent per local regulations and legal requirements, IRB / IEC often grants a waiver of consent for retrospective chart review studies. In order to avoid bias by exclusion of subjects that cannot be given informed consent for any reason like death, missing contact information etc., exempt from a written informed consent should be asked to Ethics Committees for such situations.

In case such a waiver is not given, prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by BI in accordance with the local data protection law (Organic Law 15/1999 of 13 December on the Protection of Personal Data). The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors appointed by BI, by appropriate IEC members, and by inspectors from regulatory authorities.

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

eCRF will be provided by the CRO via remote data capture. All of the clinical data and site/investigator characteristics will be captured via a web-based Electronic Data Capture (EDC) system. The site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained.

Individual patient medical information obtained as a result of this study is considered confidential. Patients must not be identified on the eCRF by name. Appropriately coded identification (i.e. Patient numbers) must be used. Any supporting documentation must be redacted of any patient identifying information and the patient ID number must be clearly written on the documents.

The investigator / institution will permit study-related monitoring, audits, IEC review and regulatory inspection, 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 available at all times for review by the sponsor's auditor and inspection by health authorities (e.g. AEMPS).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Even though this NIS is based on already existing (retrospective) data, AE management and AE reporting becomes relevant as data extraction from patient's individual medical records will be performed (study data collection) and reviewed. AE management and reporting has to be implemented and followed as outlined in this section.

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (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 adverse event 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 reaction
An adverse reaction 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 adverse event 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 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 judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the 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 (AESI)
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.

The following are considered as AESIs:

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 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 eCRF during the study data collection period:

- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome

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.

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 adverse event. An adverse reaction, in contrast to an adverse event, 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 etiologies** that could explain the event (e.g. preexisting 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, taking into account 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).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Pregnancy:
In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Ofev®, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy
The following must be reported by the investigator on the NIS AE form during the study data collection period. The starting point is the date of data extraction:

Type of Report	Timeline
All **serious ADRs** associated with Ofev®	immediately within 24 hours
All **AEs with fatal outcome** in patients	immediately within 24 hours

exposed to Ofev®	
All **non-serious ADRs** associated with Ofev®	7 calendar days
All **pregnancy monitoring** forms	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 fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate eCRF pages and the NIS AE form.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than the Ofev® administered for IPF according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be published in a national journal and presented in both regional and national pneumology conferences. A publication plan will be prepared.

13. REFERENCES

13.1 PUBLISHED REFERENCES

1. King TE, Jr., Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011; 378(9807): 1949-61.
2. Nalysnyk L, Cid-Ruzafa J, Rotella P, Esser D. Incidence and prevalence of idiopathic pulmonary fibrosis: review of the literature. Eur Respir Rev. 2012 Dec 1;21(126):355-61
3. Xaubet A, Ancochea J, Bollo E, Fernandez-Fabrellas E, Franquet T, Molina-Molina M, Montero MA, Serrano-Mollar A. Guidelines for the diagnosis and treatment of idiopathic pulmonary fibrosis. Sociedad Espanola de Neumologia y Cirugia Toracica (SEPAR) Research Group on Diffuse Pulmonary Diseases. Arch Bronconeumol. 2013; 49(8): 343-53.
4. Kim HJ, Perlman D, Tomic R. Natural history of idiopathic pulmonary fibrosis. Respir Med. 2015; 109(6): 661-70.
5. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, Colby TV, Cordier JF, Flaherty KR, Lasky JA, Lynch DA, Ryu JH, Swigris JJ, Wells AU, Ancochea J, Bouros D, Carvalho C, Costabel U, Ebina M, Hansell DM, Johkoh T, Kim DS, King TE, Jr., Kondoh Y, Myers J, Muller NL, Nicholson AG, Richeldi L, Selman M, Dudden RF, Griss BS, Protzko SL, Schunemann HJ. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med. 2011; 183(6): 788-824.
6. Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, Brozek JL, Collard HR, Cunningham W, Homma S, Johkoh T, Martinez FJ, Myers J, Protzko SL, Richeldi L, Rind D, Selman M, Theodore A, Wells AU, Hoogsteden H, Schunemann HJ. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015; 192(2): e3-19.
7. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, Kolb M. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. European Respiratory Journal. 2015; 45(5): 1434-45.
8. Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Flaherty KR, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, Le Maulf F, Girard M, Stowasser S, Schlenker-Herceg R, Disse B, Collard HR. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370(22): 2071-82.
9. Nathan SD, Shlobin OA, Weir N, Ahmad S, Kaldjob JM, Battle E, Sheridan MJ, du Bois RM. Long-term course and prognosis of idiopathic pulmonary fibrosis in the new millennium. Chest. 2011; 140(1): 221-9.

10. Bestall JC,Paul EA,Garrod R,Garnham R,Jones PW,Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax, 54 (1999), pp. 581-586

13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The stand-alone documents for this non-interventional study are:

- Statistical Analysis Plan (SAP)
- Data Management Plan (DMP)
- Serious Adverse Event Report in Non-Interventional Studies (NIS (S)AE Form)
- Pregnancy Monitoring Form

All of the above documents will be archived in the Trial Master File in its original master version.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A multicenter, retrospective chart review study to describe the clinical profile of idiopathic pulmonary fibrosis (IPF) patients treated with nintedanib (OFEV®) in real-world practice in Spain

Study reference number:
1199-0295

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]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6

[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.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

The duration of the study is less than a year.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Exploratory study

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.7.1
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
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)	☒	☐	☐	11

Comments:

Descriptive study. No measures of occurrence or association measures are performed

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2 + 9.3.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.3.1
4.2.2 Age and sex?	☒	☐	☐	9.11
4.2.3 Country of origin?	☐	☒	☐	
4.2.4 Disease/indication?	☒	☐	☐	9.11
4.2.5 Duration of follow-up?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.11

Comments:

Retrospective chart review study.

Section 5: Exposure definition and measurement	**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)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.3.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Observational study. Patients treated as per routine clinical practice.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3

Comments:

Descriptive outcomes

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.12
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

This study is only descriptive

Section 8: Effect modification	**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)	☐	☐	☒	

Comments:

This study is only descriptive

Section 9: Data sources	**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)	☒	☐	☐	9.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.3 Covariates?	☐	☐	☒	
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)	☒	☐	☐	9.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

General practice prescribing

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.3.2
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.12
12.1.2 Information bias?	☒	☐	☐	9.9
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)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

This study is only descriptive

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

APPROVAL / SIGNATURE PAGE

Document Number: c17367432 **Technical Version Number:1.0**

Document Name: clinical-trial-protocol-version-01

Title: A multicentre, retrospective chart review study to describe the clinical profile of idiopathic pulmonary fibrosis (IPF) patients treated with nintedanib (OFEV) in real-world practice in Spain.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Medical		11 May 2017 15:18 CEST
Approval-Team Member Medical Affairs		12 May 2017 14:34 CEST
Approval- Safety Evaluation Therapeutic Area		15 May 2017 10:50 CEST
Approval- of Global Epidemiology		19 May 2017 17:12 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed