Boehringer Ingelheim

Study report for non-interventional studies based on existing data

Document Number:	**c27456560-01**
BI Study Number:	1199-0295
BI Investigational Product(s):	nintedanib (OFEV®)
Title:	BROAD 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".
Version identifier of the final study report:	1.0
Date of last version of the final study report:	07 May 2019
PASS:	No
EU PAS register number:	NCT03281200 EUPAS19384
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 was 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 was 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 were: - 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 of study:	Spain
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Marketing authorization holder(s):	<u>This study is initiated, managed and sponsored by:</u> Boehringer Ingelheim España, S.A C/ Prat de la Riba, 50 08174 Sant Cugat del Vallés (Barcelona) <u>MAH:</u> Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein
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1. ABSTRACT

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Name of finished medicinal product: OFEV®			
Name of active ingredient: Nintedanib			
Report date: 07 May 2019	**Study number:** 1199-0295	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
Title of study:	BROAD 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".		
Keywords:	Idiopathic pulmonary fibrosis (IPF), Nintedanib, Forced Vital Capacity (FVC), Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO)		
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 since December 2015. There was no available data on its use in routine clinical practice after its marketing authorization before this study.		
Research question and objectives:	The present study was 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 was 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 existed, the stratification published by Nathan *et al.* (1) based on pulmonary function impairment and survival differences was applied in the study. Patients were classified with regards to the FVC and DLCO serving as surrogates for severity: FVC: - Mild IPF: FVC ≥ 70% predicted[1] - Moderate IPF: FVC 50% to 69% predicted[1] **(*)** - Severe IPF: FVC < 50% predicted **(*)** [1]FVC thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding FVC value of 70%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report.		

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	(*) %FVC has been adapted from the proposed stratification by Nathan et al from 55 to 50% to be aligned with the value used as exclusion criteria in the INPULSIS trials. DLCO: - Mild IPF: DLCO ≥50% predicted[1] - Moderate IPF: DLCO 35% to 49% predicted[1] - Severe IPF: DLCO <35% predicted [1]DLCO thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding DLCO value of 50%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report. The **secondary objectives** were: ● 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%).
Study design:	Non-interventional study based on medical charts of multiple centers, of IPF patients treated with nintedanib (OFEV®). Patients were 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, were selected.
Setting:	32 Pulmonology Services of Hospitals in Spain were the source of data collection, which were selected according to previous experience in clinical trials, NPU program, and access to nintedanib (OFEV®).
Subjects and study size, including dropouts:	Every physician was required to enrol 5 patients by site based on a simple random sampling meeting each of the following inclusion criteria and none of the following exclusion criteria. Inclusion criteria were: 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 3. The patient is newly initiated on treatment with nintedanib (OFEV®) since 01 January 2016 up to end of data collection date, according to the approved local SmPC. Exclusion criterion was:

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	1. Patients treated with nintedanib within a clinical trial or named-patient program or with any prior treatment of nintedanib. From the initially planned 175 patients, 173 were finally included. One of these patients was excluded from the analysis for not meeting the screening criteria.		
Variables and data sources:	All variables were obtained from medical records: - IPF diagnosis: method of diagnosis, date of diagnosis, UIP pattern [(according to international guideline, Raghu *et al*. 2011 (9)]. - 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 (13). - 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). Data was collected by the Investigator from patient medical records and was entered to an electronic case report form (eCRF) which included all the study variables.		
Results:	1. Primary objective. The distribution of patients across different lung function categories (%FVC and %DLCO as markers for IPF severity) at the time of treatment initiation found in the study was as it is showed in the following tables (Table 1 and Table 2):		

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Table 1: IPF stratification as per %FVC.

% FVC predicted	% (N) (I)
Mild IPF: FVC ≥ 70%[1]	57.0 (98)
Moderate IPF: FVC between 50% and 69%[1] [(*)]	38.4 (66)
Severe IPF: FVC < 50%	4.7 (8)

[1]FVC thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding FVC value of 70%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report

[(*)]%FVC has been adapted from the prosed stratification by Nathan et al from 55 to 50% to be aligned with the value used as exclusion criteria in the INPULSIS trials

(I) % values do not sum 100% due to the rounding off

Table 2: IPF stratification as per %DLCO.

% DLCO predicted	% (N)
Mild IPF: DLCO ≥ 50%[1]	42.5 (65)
Moderate IPF: DLCO between 35% and 49%[1]	35.3 (54)
Severe IPF: DLCO < 35%	22.2 (34)

[1]DLCO thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding DLCO value of 50%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report.

2. Secondary objectives.

2.1. First of secondary objectives.

The description of patient demographic and clinical baseline characteristics of the patient are summarized through the upcoming sections.

2.1.1. Sociodemographic data.

The average (± SD) age calculated for all the 172 patients at the beginning of the nintedanib treatment was 70.1 ± 8.1 years old. Besides, 23.4% (N=40) of 171 patients were females and 76.6% (N=131) were males (no gender data was collected for one patient). The 98.8% (N=170) of 172 patients were Caucasian, 0.6% (N=1) were Asiatic and 0.6% (N=1) were Arab.

2.1.2. Anthropometric and baseline clinical characteristics.

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Data on the physical examination is displayed in the following Table 3:

Table 3: Physical examination.

Variable (units)	Mean ± SD	N
Weight (kg)	77.1 ± 13.2	160
Height (cm)	164.5 ± 8.9	159
BMI (kg/m^2)	28.4 ± 3.8	159
6MWT (m)	421.7 ± 118.6	136

In reference to the smoking habit, it was found that 64% of 172 patients were former smokers whereas 2.9% were active smokers. Regarding the breathlessness grade exploration of 169 patients, results indicated that 94.7% of them suffered from dyspnea. The distribution of 160 of these patients in function of its m-MRC dyspnea scale was analized, finding the following frequencies: grade 0, 0.6%; grade 1, 40%; grade 2, 41.9%; grade 3, 15.0%; and, grade 4, 2.5%.

2.1.3. IPF medical history.

The average (± SD) of the duration of the disease (time from diagnosis until the beginning of the nintedanib treatment) recorded for all the 172 patients was 1.5 ± 3.8 years. Also, for the whole population included in the study it was found that 15.7% of it suffered from emphysema.

In reference to IPF diagnosis, the main procedures and the corresponding distribution of all 172 patients were as it is shown in the following Table 4 [NOTE: each patient might have been subject of several diagnostic procedures].

Table 4: Procedures for IPF diagnosis.

Procedures	%
High-resolution computed axial tomography	87.8
Interdisciplinary team discussion	53.5
Surgical lung biopsy	25.0
Cryosbiopsy	7.6

Finally, it was found that 12% of patients have suffered from at least one episode of acute exacerbation of the disease in the year prior to the

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nintedanib treatment initiation, being the mean number of acute episode exacerbation (± SD) 1.3 ± 0.7 exacerbations.

2.1.4. IPF treatment data.

The initial dose of nintedanib recorded for 171 patients (no initial dose of nintedanib data was collected for one patient) was 150 mg/12 h for 88.9% of them and 100 mg/12 h for 11.1%. Before this treatment, 16.6% of 169 patients recorded had been treated with pirfenidone and 11.8% of 170 individuals had taken another IPF therapy. Main treatments and the percentage of patients who received each one were acetylcysteine 5.8%, prednisone 3.5% and azathioprine 2.9% [NOTE: each patient might have been received more than one treatment].

2.1.4. Concomitant treatments.

It was recorded that 79.7% of the 172 patients enrolled in the study were taking some concomitant medication. Main treatments are summarized in the following tables (Table 5, by therapeutic groups, and Table 6, single tratments) [NOTE: each patient might have been received more than one treatment].

Table 5: Concomitant medication by therapeutic group.

Therapeutic group	**%**
Antihypertensives	76.3
Peptic ulcer and gastro-oesophageal reflux disease (GORD)	54.3
Lipid modifying agents	48.0
Treatments for pulmonary disease or IPF associated symptoms	30.5
Treatment for diabetes	26.3
Antithrombotic / Antiplatelet agents	21.9
Antidepressants	13.8
Anxiolytics	13.1

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Table 6: Concomitant medication by specific treatment.

Treatment	**%**
Omeprazole	23.3
Simvastatin	16.9
Acetylsalicylic acid	15.1
Atorvastatin	10.5
Pantoprazol	10.5
Metformin	9.9
Allopurinol	7.6
Bisoprolol	6.4
Levothyroxine	5.8
Losartan	5.2

2.2. Second of secondary objectives.

The description of the distribution of the whole population by the main comorbidities recorded is shown in the following Table 7 [NOTE: each patient might have been suffered from more than one concomitant disease]:

Table 7: Comorbidities.

Condition	**%**
Hypertension	45.9
Dyslipidaemia	42.4
Gastroesophageal reflux	25.6
Diabetes mellitus	19.8
Emphysema	15.7
Cardiovascular disease	15.7
Obstructive sleep apnoea	11.6
Pulmonary hypertension	5.8
Lung cancer	1.7
Pulmonary infection	1.2

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2.3. Third of secondary objective.

To describe the distribution of patients across different lung function categories based on the reimbursement threshold, as it happened with the primary objective, IPF stratification as per FVC was re-defined. Frequencies according to these categories are summarized in the following Table 8:

Table 8: IPF stratification as per %FVC (reimbursement threshold)

% FVC predicted	**%**
FVC > 80%	33.1
FVC between 50% and 80%.	62.2
FVC < 50%	4.7

3. Adverse Event management.

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 was performed (study data collection) and reviewed. The following tables (Table 9, Table 10 and Table 11) compile data about serious and non-serious ADRs and fatal AEs recorded during the study:

Table 9: Number of patients with Adverse Events (AE)

	N	**%**
Patients with at least one AE	60	34.9
Patients with at least one serious AE (SAE)	13	7.6
Patients with at least one AE related to nintedanib (ADR)	52	30.2

Table 10: Number of Serious Adverse Events (SAE) with fatal outcome, Serious Adverse Drug Reactions (SADR) and non-serious Adverse Drug Reactions (ADR)

	N
Number of SAE with fatal outcome	10
Number of SADR	5
Number of non-serious ADR	80

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Table 11: Number and frecuency of patients with ADR

ADR	N	% (*)
Diarrhoea	38	22.1
Nausea	7	4.1
Alteration of liver function	5	2.9
Hypertransaminasaemia	5	2.9
Vomiting	5	2.9
Weight loss	5	2.9
Abdominal pain	4	2.3
Hepatotoxicity	2	1.2
Others	13	7.8

(*) Percentages calculated on the total number of `patients analysed (N = 172)

Discussion:

The primary objective of this study aimed to describe the distribution of patients according to their lung function impairment at baseline, although clear criteria for staging IPF as per patient baseline pulmonary physiology are still to be defined. The BROAD study has therefore used the stratification previously described by Nathan *et al.* (1), based on variables %FVC and %DLCO. The distribution of patients stratified according to these variables, show that nintedanib treatment has covered a wide range of IPF severities, including those individual with more advanced lung function impairment, namely FVC <50% and or DLCO<35%.

The secondary objective of the study was to detail baseline and clinical characteristics of the population sample. Even though a direct link between ethnic and/or geographic factors and IPF prevalence has not yet been described, some of the characteristics are in line with other studies (1) (2). The high percentage of cardiovascular risk factors and gastroesophageal reflux detected within the population is also a common feature when studying IPF comorbidities (2) (3) (4).

Marketing Authorisation

MAH:
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Binger Straße 173

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Holder(s):	55216 Ingelheim am Rhein <u>This study is initiated, managed and sponsored by:</u> Boehringer Ingelheim España, S.A C/ Prat de la Riba, 50 08174 Sant Cugat del Vallés (Barcelona)		
Names and affiliations of principal investigators:	Dr. Alberto Beiztegui Sillero - Hospital Universitario Virgen de Valme (Sevilla) Dr. Álvaro Casanova - Hospital de Henares (Madrid) Dra. Ana Villar Gómez - Hospital Vall d´Hebron (Barcelona) Dr. Antonio León Jiménez - Hospital Universitario Puerta del Mar (Cádiz) Dra. Belen Mª Núñez Sánchez - Hospital Son Espases (Balears) Dr. David Iturbe Fernandez - Hospital Valdecilla (Santander) Dra. Eva Balcells Vilarnau – Hospital del Mar (Barcelona) Dr. Francisco Luis García Gil - Hospital Universitario Reina Sofía (Córdoba) Dr. Francisco Villegas Fernandez - Hospital Gomez Ulla (Madrid) Dr. Jaime Corral Peñafiel - Hospital Universitario San Pedro de Alcántara (Cáceres) Dr. Javier Villuela Bayon - Hospital Virgen del Camino (Pamplona) Dr. Jesus Arribas Barcelona - Hospital Miguel Servet (Zaragoza) Dr. Jose Ángel Figuerola Mendal - Hospital Clinico Blesa (Zaragoza) Dr. Jose Antonio Rodríguez Portal - Hospital Virgen del Rocio (Sevilla) Dr. José Antonio Ros Lucas - Hospital Clínico Universitario Virgen de la Arrixaca (Murcia). Dr. Jose Antonio Cascante Rodrigo - Hospital Virgen del Camino (Pamplona) Dr. José Belda Ramirez - Hospital Arnau de Vilanova (Valencia) Dr. José Norberto Sancho Chust - Hospital Universitario Sant Joan d'Alacant (Alicante) Dr. Jose Manuel Cifrian Martinez - Hospital Valdecilla (Santander) Dr. Juan Suárez Antelo - Hospital Universitario de Santiago (Coruña) Dr. Laura Tomas Lopez - Hospital Txagorritxu (Álava) Dr. Luis Gomez Carrera - Hospital de la Paz (Madrid) Dr. Luis Miguel Miravet Sorribes - Hospital La Plana (Castellón) Dr. Maria Teresa Rio Ramirez - Hospital de Getafe (Madrid) Dr. Miguel Bentabol Manzanares - Hospital de La Axarquía (Málaga) Dra. Miren Begoñe Salinas Lasa - Hospital Basurto (Vizcaya) Dr. Raúl Godoy Mayoral - Hospital General Albacete (Albacete) Dra. Rosana Blavia Aloy - Hospital Moisès Broggi (Barcelona) Dr. Sergio Curi Chercoles - Hospital Virgen del Camino (Pamplona) Dr. Pedro Luis Cabrera Navarro - Hospital Universitario de Gran Canaria Dr. Negrin (Las Palmas de Gran Canaria) Dra. Victoria Villena Garrido - Hospital Doce de Octubre (Madrid)		

2. LIST OF ABBREVIATIONS

6MWT	6 Minutes Walking Test
AE	Adverse Event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
ACEI	Angiotensin-converting-enzyme inhibitor
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
CLL	Chronic lymphocytic leukaemia
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
eCRF	Electronic Case Report Form
CRO	Contract research organisation
DILD	Diffuse interstitial lung disease
DLCO	Diffusing capacity of the lungs for carbon monoxide
DMP	Data Management Plan
EDC	Electronic Data Capture
EudraCT	European Clinical Trials Database
EU-QPPV	European Qualified Person for Pharmacovigilance
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced vital capacity
GIST	Gastrointestinal stromal tumor
GPV CTC	Global Pharmacovigilance Clinical Trial Coordinator
HRCT	High-resolution Chest Tomography
IEC	Independent Ethics Committee
IPF	Interstitial Pulmonary Fibrosis
IgG	Immunoglobulin G
IRB	Institutional Review Board
IPF	Idiopathic pulmonary fibrosis
KCO	Carbon Monoxide Transfer Coefficient
LPVM	Local Pharmacovigilance Manager
MAH	Marketing Authorization Holder
Max	Maximum
Min	Minimum
mMRC	Modified Medical Research Council
N	Number of patients
ND	Not documented
NPU	Named patient use
NIS	Non-Interventional Study
OSAS	Obstructive sleep apnoea syndrome
PASS	Post authorization Safety Study
Q1	First quartile
Q3	Third quartile
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAP	Statistical Analysis Plan
SD	Standard Deviation
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
SPSS	Statistical package for the social sciences
TKI	Tyrosine kinase inhibitor
UIP	Usual interstitial pneumonia

3. INVESTIGATORS

The coordinating investigators were:

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Pulmonology Department

and

Dr Álvaro Casanova
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The physicians performed the NIS in accordance with the protocol (available as a stand-alone documents, see Section 15. Appendices), applicable local regulations, and international guidelines.

A list of all participating principal investigators is displayed in the Table 12 below:

Table 12 Participating Principal Investigators in the study.

Name	Affiliation
Dr. Alberto Beiztegui Sillero	Hospital Universitario Virgen de Valme (Sevilla) Pulmonology Department
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Dra. Victoria Villena Garrido	Hospital Doce de Octubre (Madrid) Pulmonology Department

4. OTHER RESPONSIBLE PARTIES

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Boehringer Ingelheim España. Medical Affairs.

Medical Advisor: Cristina Moro
Boehringer Ingelheim España. Medical Affairs.

Project Manager: Mireia Canals
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CRO Clinical Team Leader: Cristina Larios
CRO Biostatistician: Laura Casas
CRO Medical Writer: Carlos Alonso

5. MILESTONES

Table 13 Milestones

Milestone	Planned date	Actual date	Comments
IEC approval		15 Jun 2017	Coordinator Investigator site: Hospital Universitario Virgen del Rocío (Sevilla)
Start of data collection	01 Sep 2017	21 Oct 2017	Sites were gradually opened as it was obtained all requirements (CEIC authorization, CDC and contract) and in accordance to PI availability. Thus, three first sites were opened by 21st of September and first patient was included on 21st of October.
End of data collection	30 Dec 2017	June 2018	Inclusion period ended up in January, whereas database closed by June. This was mainly due to a delay in data resolution, as it was generated some pharmacovigilance discrepancies.

Milestone	Planned date	Actual date	Comments
Registration in the EU PAS register	May 2017	Jun 2017	EU PAS Register no. 19384
Final report of study results	March 2018	14 Nov 2018	The database was locked in June 2018. The statistical report was finished on 14 November 2018.

6. 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 (5). 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 space (6). Based on this data, it is believed that, in Spain, IPF could be affecting around 7500 people (7). 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 (8).

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 (9) [updated on treatment recommendations in 2015(10)] 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 (9). 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 (11).

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

(12) and INPULSIS-2 (11)]. 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 mL in placebo group and -114.7 ± 15.3 mL 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 mL in placebo group and -113.6 ± 15.73 mL in the nintedanib group ($p<0.0001$). These results led to its approval on 15th January 2015 by the European Commission for the treatment of IPF in adults.

In 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, in 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 UIP pattern. On 15th 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. In 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.

7. RESEARCH QUESTION AND OBJECTIVES

The present study was 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 was 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*. (1) based on pulmonary function impairment and survival differences was applied in the study:

1. FVC:
   - Mild IPF: FVC ≥ 70% predicted[1]
   - Moderate IPF: FVC 50% to 69% predicted[1] **(*)**
   - Severe IPF: FVC < 50% predicted **(*)**

[1]FVC thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding FVC value of 70%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report
(*) %FVC has been adapted from 55 to 50% to be aligned with nintedanib (OFEV®) clinical trials program.

2. DLCO:
- Mild IPF: DLCO ≥50% predicted[1]
- Moderate IPF: DLCO 35% to 49% predicted[1]
- Severe IPF: DLCO <35% predicted

[1]DLCO thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding DLCO value of 50%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report.

The secondary objectives were:
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%).

8. AMENDMENTS AND UPDATES

None

9. RESEARCH METHODS

9.1 STUDY DESIGN

This non-interventional study, based on medical charts, was conducted in 32 Pulmonology Services of Hospitals in Spain. IPF patients were characterized at time of nintedanib initiation (cross-sectional study design).
The participating investigators reviewed their IPF patient's medical records since 1st 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 random sampling was applied. The Investigator shared an anonymized list of all of hers/his patients who met selection criteria with the CRO. The list included the minimum patient data to be identifiable by the investigator, for example, age, gender and treatment initiation date. Then, CRO had generated a random sequence of the 5 patients to be included and informed the Investigator.
As this was a non-interventional study, designed to reflect real-world clinical practice, the decision to start treatment with OFEV® had been 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, was applied to patients other than that used for routine clinical practice.

9.2 SETTING

The study was conducted by Boehringer Ingelheim España, S.A. with the participation of 32 Pulmonology Services of Spanish hospitals distributed throughout Spain. These sites were selected according to previous experience in clinical trials, named-patient programs, and access to nintedanib (OFEV®).

According to the local legislation of observational studies, the protocol was classified by the Spanish Health Authority as an "EPA-OD: Estudio Post autorización- otros diseños" (Post-authorization study- other designs). It was also approved by the Ethics Committee of the Hospitales Universitarios Virgen Macarena and Virgen del Rocío. Authority classification and Ethics approval are attached as appendix 3 respectively.

The protocol was requested to be evaluated by additional Ethics Committees of the following sites: H. Puerta del Mar, H. Virgen Macarena, H. Central de Asturias, H. Gran Canaria-Dr. Negrín, H. Mar, H. Vall Hebrón, H. Parc Taulí, H. La Mancha Centro, H. 12 de Octubre, H. La Paz, H. Gómez Ulla, H. Getafe, CEIC Euskadi, H. La Plana, H. San Juan de Alicante, H Arnau de Vilanova. These Ethics Committees also approved the study in their region of influence.
Since there has been patients not able to sign ICF at the moment of data collection due to the progression of the disease, but whose information was relevant for the study, an exemption for informed consent was requested by the sponsor and approved by all the Ethics Committees that evaluated the study except the committees from the H. Basurto and H. Txagorritxu (both IEC Euskadi) together with the Ethics Committee of the H. Parc Taulí, that requested an ICF for alive patients selected to be included.

The rights and obligations of the participating physicians and of Boehringer Ingelheim España were set out in a contract governing the performance of an NIS. The participating physicians undertook to perform the NIS responsibly in accordance with the agreements made in the contract.

Boehringer Ingelheim España compensated the participating physicians for their expenses as stated in the contract.

The information was recorded in the eCRF by the participating investigators during the study period, being the first patient included on 21st October 2017 and the last one on 31st January 2018.

9.3 SUBJECTS

Initially, it was expected to recruit approximately 175 individuals from 35 Pulmonology Services in Spain. To be eligible to participate in the study, patients should had met the following selection criteria.

1. Inclusion criteria. Patients could be included in the study if all of the following criteria were met:
  1. 1. The patient is at least 18 years old.
  1. 2. The patient has IPF diagnosis according to 2011 ATS/ERS/JRS/ALAT IPF guideline for diagnosis and management (9).
  1. 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.

2. Exclusion criteria. Patients will be excluded if the following criterion was met:
  2.1. Patients treated with nintedanib within a clinical trial or named-patient program or with any prior treatment of nintedanib.

The study ended up with 32 Pulmonology Services. Besides, from the 175 individual who were initially planned to be recruited in the study, 173 of them were finally included. One of these patients did not meet the inclusion criteria as she/he initiated *de novo* treatment with nintedanib before 1st January 2016.

9.3.1 Cases

Not applicable.

9.3.2 Controls

Not applicable.

9.4 VARIABLES

The following variables were obtained from the patient medical records:
- IPF diagnosis: method of diagnosis, date of diagnosis, UIP pattern [according to international guideline, Raghu *et al*. (9)].
- 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 (13).
  - Pulmonary function: predicted %FVC and %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).

9.4.1 Exposures

Patients in this study had been prescribed nintedanib (OFEV®) treatment for their IPF on or after 01 January 2016. Prescription of the treatment was done under the sole responsibility of the healthcare professional. The date of treatment initiation and the dose was 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 includes all type of IPF patients, independent of their pulmonary function.

9.4.2 Outcome(s)

9.4.2.1 Primary outcome(s)

The primary outcome of the study was "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".
As no established severity grading exists, the stratification published by Nathan *et al*. (1) based on pulmonary function impairment and survival differences was applied.
Patients were classified with regards to the FVC and DLCO serving as surrogates for severity:

FVC:
- Mild IPF: FVC ≥ 70% predicted[1]
- Moderate IPF: FVC 50% to 69% predicted[1] **(*)**
- Severe IPF: FVC < 50% predicted **(*)**

[1]FVC thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding FVC value of 70%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report
(*) %FVC has been adapted from 55 to 50% to be aligned with nintedanib (OFEV®) clinical trials program.

DLCO:
- Mild IPF: DLCO ≥50% predicted[1]
- Moderate IPF: DLCO 35% to 49% predicted[1]
- Severe IPF: DLCO <35% predicted

[1]DLCO thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding DLCO value of 50%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report.

The study outcomes were 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).

9.4.2.2 Secondary outcome(s)

The first of the secondary outcomes was "to describe demographic and clinical baseline characteristics of IPF patients at time of treatment initiation with nintedanib (OFEV®)".
Descriptive statistics were 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*. (9)].
- 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 (13).

- concomitant medication (active substance, dose, initiation date, indication)
- Mean Number and frequency of exacerbations due to IPF in the previous year

The second of the secondary objectives was "to describe comorbidity prevalence at time of treatment initiation: frequency of each comorbidity".
Descriptive statistics were provided for the following 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.

The third of the secondary objectives was "to describe the distribution of patients across different lung function categories based on reimbursement threshold (FVC >80%, 50-80%, and <50%)".
The stratification was defined as follows:

- FVC > 80% predicted
- FVC 50% to 80% predicted
- FVC < 50 % predicted

9.4.2.3 Further outcome(s)

Not applicable

9.4.3 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 was performed (study data collection) and reviewed.

9.4.3.1 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 unfavorable 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 tem 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 were defined for this study.

9.4.3.2 Adverse event and serious adverse event reporting

The investigator should have maintained and kept detailed records of all AEs in their patient files.

Collection of AEs

The study design was of non-interventional nature and the study was conducted within the conditions of the approved marketing authorization. Sufficient data from controlled interventional trials were 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 had been defined.

The following should have been 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 should have been followed up until they were resolved, sufficiently characterized, or no further information was possible to be obtained.

The investigator carefully assessed whether an AE constituted an ADR using the information bellow.

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:

Table 14 Reporting of AEs and Drug Exposure During Pregnancy.

Type of Report	Timeline
All **serious ADRs** associated with Ofev®	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Ofev®	immediately within 24 hours
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 have provided 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 was 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.

9.4.4 Covariates

Not applicable.

9.5 DATA SOURCES AND MEASUREMENT

Data collection was limited to those available in the medical records of selected patients. All medical records of the 32 included centers were screened for IPF patients and then patients who initiated treatment with nintedanib since 01 January 2016 up to the end of data collection date were identified. 5 patients per site were selected based on a simple random sampling of all the patients from each physician.

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

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

9.6 BIAS

In order to ensure representativeness of patients among the whole country, each Investigator included 5 patients. To minimize selection bias, a simple random sampling was applied. The Investigator shared an anonymized list of all of his patients who had met selection criteria with the CRO. The list included the minimum patient data to be identifiable by the investigator, for example, age, gender and treatment initiation date. Then, CRO generated a random sequence of the 5 patients to be included and informed the Investigator.

9.7 STUDY SIZE

The following Table 15 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 was assumed to be 10% for all scenarios.
Precision is estimated based on two-sided 95% confidence intervals.

Table 15 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 are recruited.
Planning a recruitment of 175 patients would allow for an acceptable precision of prevalence of a specific lung function profile (see Section 9.4.2.1) estimates.

9.8 DATA TRANSFORMATION

The data were entered by the investigators themselves and/or authorized personnel directly in the electronic case report form (eCRF). The eCRFs included programmable edits to obtain immediate feedback if data were missing, out of range, illogical or potentially erroneous.
The database was housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system met the standards of the International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality was strictly maintained.
Once the study has been completed and all data from the last patient have been recorded, the database was closed and statistical analysis was performed.

9.9 STATISTICAL METHODS

The proposed methods for statistical analysis presented below are a summary of the methods that were applied in the study to analyze the data collected and to answer the study objectives. Missing data was not imputed in the main analysis. The detailed planned analyses are provided in the final Statistical Analysis Plan (SAP), v 0.3 dated on 9th of February of 2018, available as a stand-alone document.

Analyses was performed by the CRO Dynamic Science S. L.
Data was analyzed using SPSS v22.0.

9.9.1 Main summary measures

For the summarizing the primary outcome accomplishment, as it involves qualitative variables, the absolute and relative frequencies of patients were employed. For the first of the secondary objectives, absolute and relative frequencies were used to describe the qualitative variables, and measures of central tendency and dispersion [mean, median, standard deviation (SD), first quartile (Q1) and third quartile (Q3), minimum and maximum] for the quantitative variables. For accomplishment of the second and third of the secondary objectives, both involving qualitative variables, it was turned to absolute and relative frequencies.

9.9.2 Main statistical methods

Since the study design is cross-sectional, descriptive statistics were used for summarizing data of quantitative variables through measures of central tendency and dispersion: mean, median, standard deviation (SD), first quartile (Q1) and third quartile (Q3), minimum and maximum. In some cases, the 95% confidence interval was given. On the side of the qualitative variables, the description was carried out by absolute and relative frequencies.

9.9.3 Missing values

Absences of data were not accounted for and were considered missing data.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 QUALITY CONTROL

To improve and secure data quality, automatic data checks upon data entry were done within the eCRF. In the eCRF, plausible ranges of values for numeric data entries as well as logical data entries and listings were provided for each entry field. Based on this, checks on completeness and plausibility were performed upon data entry in the eCRF.
Validity of data entry thus was ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the document list or investigator. All corrections were visible from the system audit trail.
No regular source data verification was 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 might have been performed, but was finally not considered necessary to be performed.
In addition, a quality assurance audit/inspection of his study might have been conducted by the sponsor or sponsor's designees or by Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor may have had access to all medical records, the investigator's study-related files and correspondence, and the informed consent document (if applicable).
Finally, despite the retrospective design of the study, the reconciliation for the defined adverse events collected (all serious and non serious adverse drug reaction (ADRs) and- all AEs with fatal outcome) was performed.

10. RESULTS

10.1 PARTICIPANTS

It was expected to recruit approximately 175 individuals from which 173 were finally included. One of these patients did not meet the inclusion criteria as she/he initiated *de novo* treatment with nintedanib before the 1st of January of 2016, so the final number of patients included in the study was 172.

10.2 DESCRIPTIVE DATA

Since the 1st of the secondary objectives is "to describe the demographic and clinical baseline characteristics of IPF patients at the time of treatment initiation with nintedanib (OFEV®)" (see Section 9.4.2.2), the characteristics of the study subjects are being displayed below in Section 10.4.2.1 "First of secondary outcomes".

10.3 OUTCOME DATA

This was a cross-sectional epidemiological study where no diagnostic or therapeutic intervention was applied so that the clinical outcome of patients was not a factor under

investigation. Given the design of the study, there was not a follow-up period to study the clinical outcome of patients.

10.4 MAIN RESULTS

10.4.1 Primary Outcome(s)

The primary objective of the study was "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".
To accomplish this outcome and since there is not any consolidated severity classification, it was taken the stratification published by Nathan *et al*. (1), which it is founded on pulmonary function and survival differences. Consequently, it has been defined for %FVC
the following categories/variables:

- Mild IPF: FVC ≥ 70% predicted[1]
- Moderate IPF: FVC between 50% and 69% predicted[1]
- Severe IPF: FVC < 50% predicted[(*)]

[1]FVC thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding FVC value of 70%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report
[(*)] %FVC has been adapted from 55 to 50% to be aligned with nintedanib (OFEV®) clinical trials program.

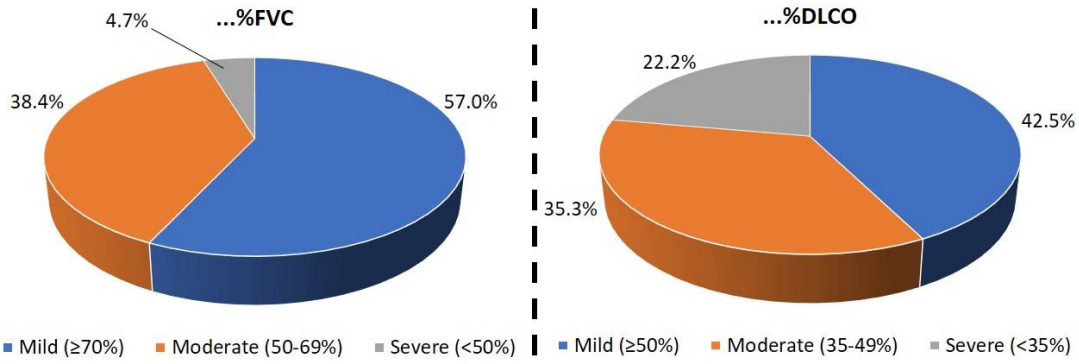
Analogously, for %DLCO, it has been defined the categories/variables:

- Mild IPF: DLCO ≥ 50% predicted[1]
- Moderate IPF: DLCO between 35% and 49% predicted[1]
- Severe IPF: DLCO < 35% predicted

[1]DLCO thresholds according to the stratification published by Nathan et al. were incorrectly mentioned in the study protocol Version 1.0 (11 May 2017) regarding DLCO value of 50%, which was assigned to the Moderate IPF stratum. Correct thresholds have been applied for the analysis and conclusions of the study report.

Thus, distribution of patients as per their IPF-severity according to both lung function variables is as shown in the following Figure 1.

Figure 1 Stratification of patients by function impairment



NOTE: For FVC, % values do not sum 100% due to the rounding off

10.4.2 Secondary Outcomes.

10.4.2.1 First of secondary outcomes: "To describe demographic and clinical baseline characteristics of IPF patients at time of treatment initiation with nintedanib (OFEV®)".

The following sections summarized the baseline characteristics of the patients at treatment onset.

10.4.2.1.1 Sociodemographic data.

In reference to the age of the individuals enrolled, it was collected the information at three timepoints, namely, at the baseline visit, at the diagnosis and at the treatment initiation, being the mean (± SD) for all the 172 patients recruited 71.0 ± 8.1, 68.9 ± 8.1 and 70.1 ± 8.1 years old, respectively. Regarding the gender distribution (N=171), it was found that 23.4% (N=40) were women and 76.6% (N=131) were males. Finally, and regarding the race distribution, it was found that almost all the 172 individuals were Caucasian (*i.e.* 98.8%), only 0.6% (N=1) were Asiatic and 0.6% (N=1) were Arab.

10.4.2.1.2 Anthropometric and baseline clinical characteristics.

It was collected data about the physical examination and other relevant clinical variables, such as the smoking habit, at the time of the nintedanib treatment onset for the majority of the individuals recruited. Main of these varialbles are summarized in the following Table 16:

Table 16 Anthropometric and baseline clinical characteristics

Variable	**Value**
Weight [(kg), (N = 160), mean ± SD]	77.1 ± 13.2
Height [(cm), (N = 159), mean ± SD]	164.5 ± 8.9
BMI [(kg/m^2), (N = 159), mean ± SD]	28.4 ± 3.8
6MWT [(m), (N = 136), mean ± SD]	421.7 ± 118.6
Breathlessness (N = 160)	
Frecuency of patients suffering from dysnea (%):	94.7
Distribution by dysnea grade as per m-MRC scale (%):	
Grade 0	0.6
Grade 1	40.0
Grade 2	41.9
Grade 3	15.0
Grade 4	2.5

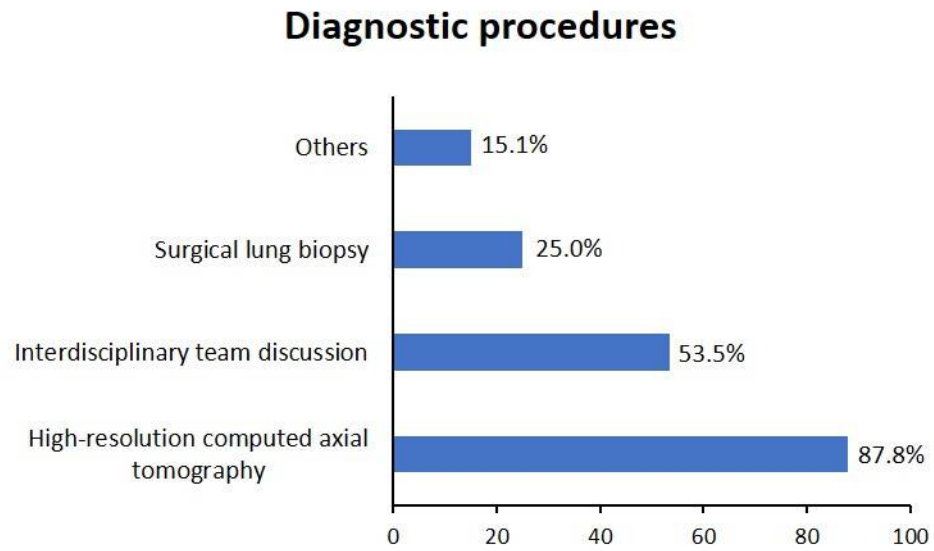
Variable	Value
Lung function exploration	
%FVC [(N = 172), mean ± SD]	74.3 ± 17.9
%DLCO [(N = 153), mean ± SD]	48.2 ± 18.0
Smoking habit	
Distribution of patients by their habit (N = 172, %):	
Never smokers	33.1
Fomer smokers	64.0
Active smokers	2.9
Number of pack-year [(N = 96), mean ± SD]*	38 ± 24.9

*This data of no. of pack-year is collected directly and is not self-calculated and therefore these values must be taken with caution when interpreting the results.

10.4.2.1.3 IPF medical history.

It was recorded the duration of the disease in years, referred as the time elapsed from the date of diagnosis until the start date of treatment with OFEV®. Thus, the mean (± SD) calculated for this variable was 1.5 ± 3.8 years. Besides, it was registered that 15.7% of the total of patients included suffered from emphysema. For the diagnosis of the disease, it was employed several procedures, and a patient could have been diagnosed by more than one procedure. In the following Figure 2 it is showed the percentage of patients who were diagnosed by each of the techniques.

Figure 2 Ditribution of patients by the procedure employed for their IPF diagnosis



NOTE: Patient may have indicated more than one type of procedure.

Furthermore, it was recorded UIP histopathological pattern for 69.7% of 76 patients and UIP radiological pattern for 90.0% of 170 patients. Finally, it was found that 12.0% of 166 patients have suffered from exacerbations of IPF in the year prior to initiating treatment, being the average (±SD) number of exacerbations over the last year before nintedanib treatment initiation 1.3 ± 0.7.

10.4.2.1.4 IPF treatment data.

In reference to nintedanib treatment at its onset, it was recorded the initial dose administrated to 171 patients, being 150 mg/12 h for 88.9% and 100 mg/12 h for 11.1%.
Previously to this treatment, 16.6% of 169 patients had been treated with pirfenidone, being the average (±SD) dose calculated for 27 patients 702.1 ± 198.0 mg/8h. Additionally, there was data available in reference to the reason for discontinuing the pirfenidone treatment for 28 individuals, which was lack of efficacy in 28.6%, adverse event in 53.6%, investigator´s decision in 7.1% and patient´s decision in 10.7%.
Besides pirfenidone, it was found that 11.8% of 170 individuals had received other IPF treatments, which could have been medicated with more than one therapy. Frequencies recorded for the main treatments were as follows: acetylcysteine 5.8%, prednisone 3.5%, azathioprine 2.9%, deflazacort 0.6%, experimental stem cell therapy 0.6%, home oxygen therapy 0.6%, and sulfasalazine 0.6%.

10.4.2.1.5 Concomitant treatments at nintedanib treatment onset

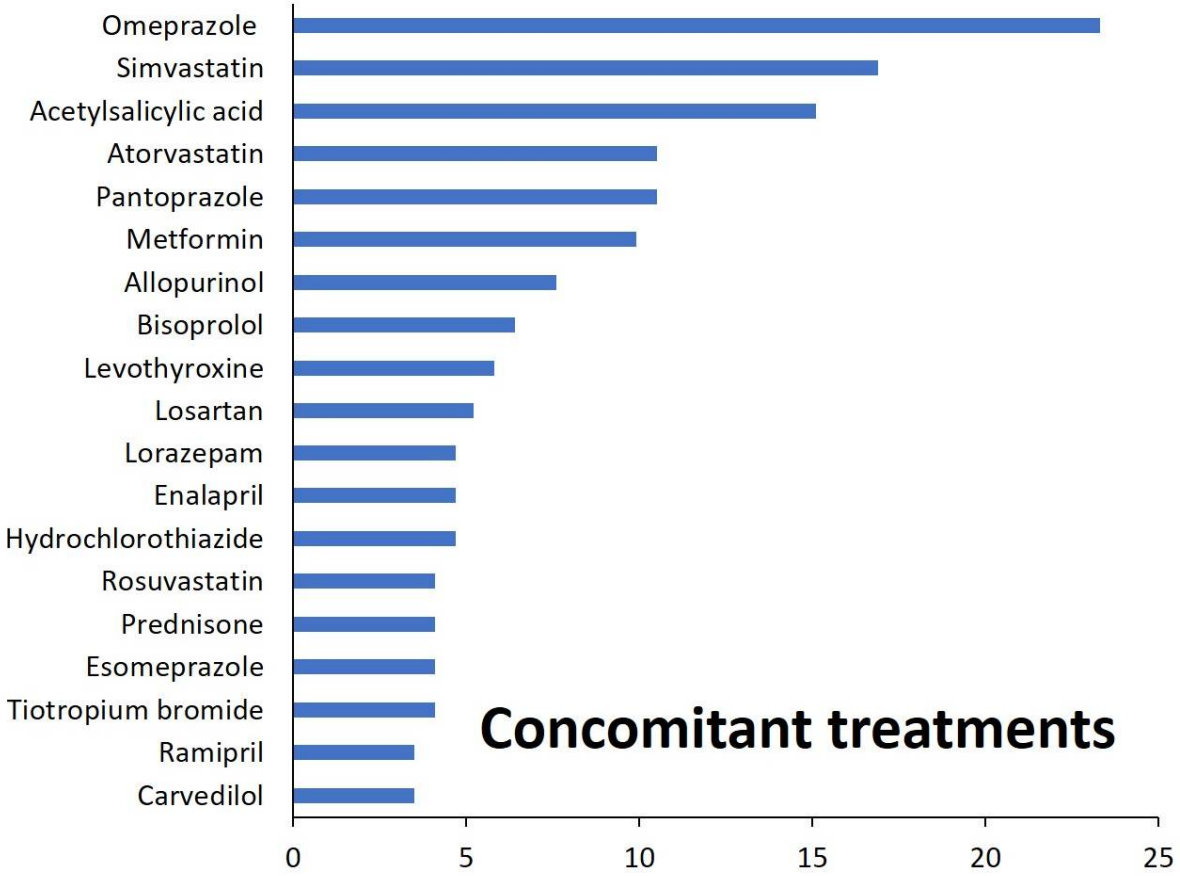
From the whole population enrolled in the study, it was found that 79.7% of the individuals was taking some concomitant medication at the nintedanib treatment onset. Besides, each one of these patients could have been receiving more than one concomitant treatment. In the following Table 17 it is compiled the frequency of patients that have been encountered for each concomitant treatment classified by the therapeutic group.

Table 17 Frequency of patients as per concomitant treatment classified by its therapeutic group

Therapeutic group	**%**
Antihypertensives	76.3
Peptic ulcer and gastro-oesophageal reflux disease (GORD)	54.3
Lipid modifying agents	48.0
Treatments for pulmonary disease or IPF associated symptoms	30.5
Treatment for diabetes	26.3
Antithrombotic / Antiplatelet agents	21.9
Antidepressants	13.8
Anxiolytics	13.1

In the Figure 3 below, it can be seen a list of medications taken by a percentage of patients above 3%.

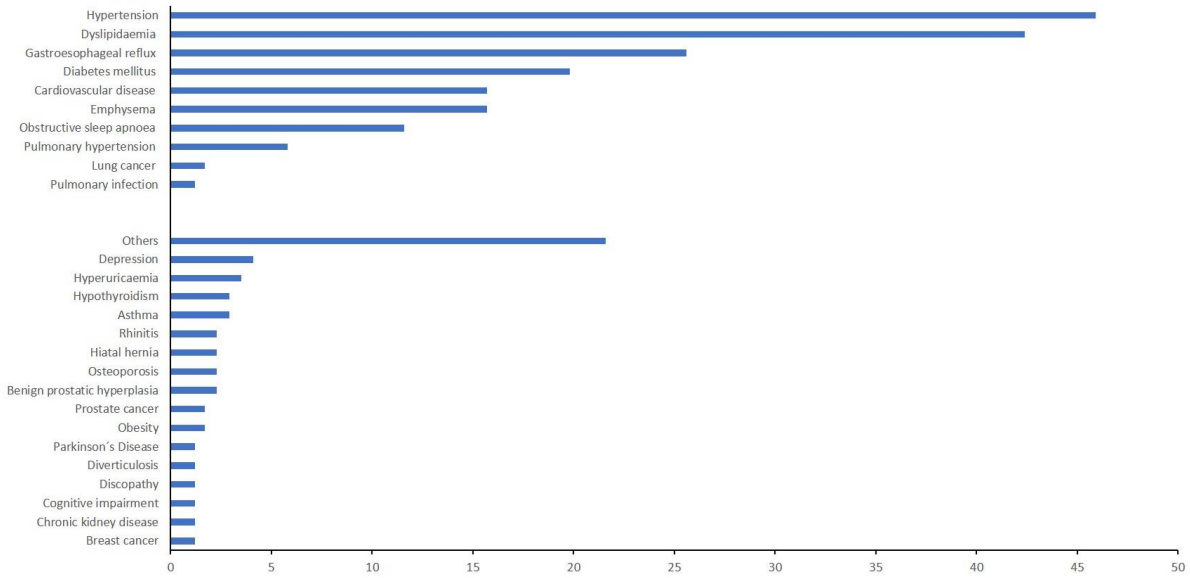
Figure 3 Patients frequency for the main concomitant medications.



10.4.2.2 Second of secondary outcomes: “To describe comorbidity prevalence at time of treatment initiation: frequency of each comorbidity”.

It was recorded the concomitant diseases patients suffered at the time of nintedanib therapy onset, being possible that a patient might have suffered from more than one of these conditions. In the Figure 4 below the frequencies found in the whole population for comorbidities are shown. In the upper part of this Figure, it is shown the patients distribution by the main comorbidities detailed in Section 9.4.2.2. Furthermore, in this study it was found that 42.1% of patients had suffered from different conditions besides the main ones. Therefore, in the lower part of the figure it can be seen the frequencies found for these conditions, showing the comorbidities for which it has been detected percentages above 1% (the sum of all the frequencies lower than 1% are grouped and named as “others”).

Figure 4 Patients frequency for the main concomitant diseases.



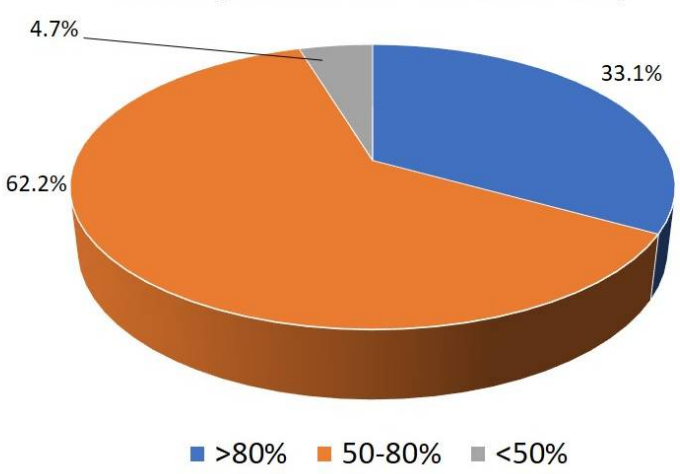
10.4.2.3 Third of secondary outcomes: "To describe the distribution of patients across different lung function categories based on the reimbursement threshold (FVC >80%, 50-80%, and <50%)".

Since the OFEV® reimbursement in Spain is for patients whose %FVC is between 50 and 80%, stratification of patients according to this parameter was as follows:

- FVC > 80%.
- FVC between 50% and 80%.
- FVC < 50%.

The distribution of patients according to these categories is shown in the following Figure 5.

Figure 5 Patients distribution by their IPF-severity stratification as per the %FVC reimbursement threshold



10.4.3 Further Outcome(s)

Not applicable

10.5 OTHER ANALYSES

None.

10.6 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 was performed (study data collection) and reviewed.
The adverse events and adverse drug reactions reported by the investigators during the study period, were classified according to preferred terms.
The following tables (Table 18, Table 19, Table 20, Table 21, and Table 22) compile data about serious and non-serious ADRs and fatal AEs recorded during the study:

Table 18 Number of patients with Adverse Events (AE)

	N	%
Patients with at least one AE	60	34.9
Patients with at least one serious AE (SAE)	13	7.6
Patients with at least one AE related to nintedanib (ADR)	52	30.2

Table 19 Number of Serious Adverse Events (SAE) with fatal outcome, Serious Adverse Drug Reactions (SADR) and non-serious Adverse Drug Reactions (ADR)

	N
Number of SAE with fatal outcome	10
Number of SADR	5
Number of non-serious ADR	80

Table 20 Fatal Serious Adverse Events (Fatal SAEs) as per patient frequency

SAE	N	% (*)
Death	2	1.16
Progressive IPF	2	1.16
Exacerbation of IPF	1	0.58
Congestive heart failure due to pulmonary arterial hypertension	1	0.58

SAE	N	% (*)
Metastasic urothelial carcinoma	1	0.58
Community-acquired pneumococcal pneumonia	1	0.58
Pneumothorax	1	0.58
Syndrome Acute coronary	1	0.58

(*) Percentages calculated on the total number of patients (N = 172).

Table 21 Serious Adverse Drug Reactions (SADR) as per patient frequency

SADR	% (*)
Weight loss	0.58
Hypertensive crisis due to poorly controlled hypertension	0.58
Hepatotoxicity	0.58
Diarrhoea	0.58

(*) Percentages calculated on the total number of patients (N = 172).

Table 22 Number and frecuency of patients with ADR

ADR	N	% (*)
Diarrhoea	38	22.1
Nausea	7	4.1
Alteration of liver function	5	2.9
Hypertransaminasaemia	5	2.9
Vomiting	5	2.9
Weight loss	5	2.9
Abdominal pain	4	2.3
Hepatotoxicity	2	1.2
Others	13	7.8

(*) Percentages calculated on the total number of `patients analysed (N = 172)

11. DISCUSSION

11.1 KEY RESULTS

The primary objective of the study was to analyze the distribution of the patients by their lung function impairment at baseline, and for that purpose, it was taken the stratification reported as per %FVC and %DLCO by Nathan *et al*. (1). Therefore, according to the first variable, namely %FVC, it was found that almost all patients were spread out within the mild (around

55%) and the moderate (around 40%) IPF. Meanwhile, according to %DLCO, 80% of the individuals seemed to be split between the mild and moderate categories (both around 40% each one), whereas 20% of them were classified within the severe category. Despite this, it might be asserted that a reasonable number of patients have started the nintedanib treatment with advanced impairment in lung function and gas exchange.

The description of the demographic and clinical baseline characteristics met by the first of the secondary objectives has permitted a perception of the general conditions in which the population enrolled in the study is. Additionally, it has provided quality data on the IPF diagnosis and treatment. Thus, it was found a sample of subjects aged in average of around 70 years old within which almost 75% of them were men and of Caucasian origin. Regarding the physical examination, it has revealed that patients might be overweight, as it is indicated by a mean BMI scoring around 28 kg/m^2, which indeed matches the punctuation obtained through the average weight and height. In reference to the description of the respiratory symptoms, the vast majority of 169 patients analyzed (around 95%) suffered from dyspnea, who where mainly distributed between grade 1 and grade 2 (both with around 40% of the patients) of the m-MRC Dyspnea Scale. Additionally, it is also quite interesting to have found that third part of the population recruited have stated they were “never smokers”.

The scrutiny of the medical history has allowed the description of the IPF disease and its approach. Thus, for instance, although IPF might have been diagnosed by multiple procedures, data recorded shows that the main technique employed was high-resolution computed axial tomography (almost 90% of the patients) followed by far by interdisciplinary team discussion (around 50% of the patients). Besides, it was found an UIP radiological pattern in 90% of 170 patients, that is almost the whole population of the study. In the whole sample it was found that a 12% of patients suffered from IPF exacerbations in the year prior to the treatment onset. About the IPF treatment, data indicated that the initial dose of nintedanib was mainly 150 mg/12 h and that approximately 16% of the patients have also received previously pirfenidone and/or 11% received other therapies.

The second of the secondary objectives aimed to describe the comorbidities associated with IPF. In this regard and aside from the lung-related complications like obstructive sleep apnoea or pulmonary hypertension, the presence of hypertension or dyslipidaemia, both cardiovascular risk factors, was highly frequent (40-45%), together with gastroesophageal reflux, diabetes mellitus and cardiovascular disease (15-25%).

Across the description of the baseline characteristics of the patients, there was the compilation of the concomitant medications that patients had been receiving at nintedanib treatment onset. In reference to this point, it seems that somehow it was related to the management of the aforementioned cardiovascular risk factors, within which it is also found the overweight condition revealed by the assessment of the anthropometric characteristics. Thus, some of the main drugs found were lipid-lowers such as atorvastatin or simvastatin, and, on another hand, metformin, which is usually prescribed for type 2 diabetes mellitus in overweight patients. Also, probably related to the management of cardiovascular risk factors as well as to the prevention of the blood hypercoagulability [which is indeed a complication reported to be a common comorbidity in IPF patients (2)] might be the high frequency found in acetylsalicylic acid. It has been also reported that around 30% of the patients were receiving treatments for pulmonary disease or IPF associated symptoms. Since within the comorbidities it has not been recorded chronic obstructive pulmonary disease (COPD) and/or asthma, it seems that the aforementioned treatments could have been prescribed for the treatment of IPF-related symptons, such as cough and dyspnea. Besides, it has been detected

the prescription of anxiolitics and/or anti-depressants, which could be related with the diagnosis and bad prognostic of the disease, as it has been reported (15). Finally, there were some frequently prescribed treatments belonging to the gastroesophageal reflux management family of drugs, such as proton pump inhibitors pantoprazole or omeoprazol. In fact, the association of this comorbidity in IPF pathogenesis has been speculated (2) (3) (4) .
Ultimately, to accomplish the last outcome of the study, namely "to describe the distribution of patients across different lug function categories based on the reimbursement threshold", as OFEV reimbursement in Spain is for patients with FVC between 50 and 80%, it was taken the %FVC-based IPF stratification as follows: FVC > 80%, FVC between 50 and 80%, and FVC < 50%. Thus, according to this FVC thresholds limitations and for the whole population of the study, one third of the patients had FVC >80% and almost two thirds had FVC between 50 and 80%. This means that one third of the patients were treated for IPF, having pulmonary function more preserved (FVC >80%), which probably means an improvement in IPF diagnosis.

11.2 LIMITATIONS

Since the present study has a cross-sectional design instead of a prospective one, the quality of data could be comprised due to the lack of all information for the whole population and for all the variables. At this point, it should be taken into account that the sample size was estimated accordingly to the primary objective, aiming to reach an acceptable precision of prevalence of a specific lung function profile (see section 9.4.2.1). The final number of assessable patients was 172, slightly below of this estimated size of 175 individuals. All the information of all these 172 patients was indeed achieved for the variables related to the primary objective and for the third of the secondary objectives, which also intended to describe a specific lung function profile. Therefore, data quality is fair enough for attaining the description of the distribution of IPF patients across their lung function profile with an acceptable precision. Also pointing out the possible adequacy of the sample size since there is a low prevalence of the disease worldwide (6), and the estimated number of IPF-patients across Spain is below 10,000 people (7).
Regarding the variables of patient physical examination, for instance, there was no availability for the complete information for all the patients recruited in the study. Thus, the precision for describing the clinical characteristics of the patients is, in those cases, lower. Nevertheless, since endpoints of the study aimed only for description of IPF patients and not to stablish any causality and/or comparison, the lack of information in principle only affects the dispersion of data (*i.e.* standard deviation).
Finally, on another hand, pointing out that although the possible selection bias has been solved through performing a random sampling (see Section 9.6), it cannot be discarded any source of informational bias (14).

11.3 INTERPRETATION

All the outcomes of this study included descriptive endpoints which were met by summarizing the distribution of the patients across the different qualitative variables and measures of central tendency and dispersion of the quantitative ones. Although in some cases there was some missing data and a larger sample size would probably strengthen the results (see previous Section 11.2), the final goal of the study was fully accomplished.

Regarding the distribution of patients at treatment onset and according to IPF severity stratification demanded by the first objective of the study, it has shown differences depending on the lung function variable employed. In other words, taking only the %FVC values for patient stratification in our cohort, there were hardly any patients suffering from severe disease, whereas by taking the %DLCO values, more patients with advanced condition could be identified. In this scenario, it should be considered the higher prognostic factor of %DLCO over %FVC pointed out by Nathan *et al*. (1) and, consequently, results suggest a considerable number of severe-IPF patients.

According to the inclusion criteria, all patients should have been receiving nintedanib, and as per the medical history, around 15% also have been receiving pirfenidone before it. Both antifibrotic drugs have been included for the treatment of IPF as they decrease the progression of the disease (2). Interestingly, almost 30% of individuals have discontinued the pirfenidone treatment because of reported lack of efficacy. In addition, although around 20% of patients were suffering from severe-IPF, for whom it should be considered a transplant therapy (2), description of the prior treatments has shown that only 1 patient have received an experimental stem cell therapy.

This cross-sectional study has permitted the description of comorbidities, showing 25% of patients suffering from gastroesophageal reflux. Recording this complication should be pretty critical since it has been linked to IPF pathogeny (2) (4). Nevertheless, presence of gastroesophageal reflux in this study is lower than the usual one of 50% (2) (3) . In reference to high percentage of patients with cardiovascular risks factors such as hypertension and/or dyslipidaemia (both around 45%), it has also been described an association of vascular disease and IPF (2) (4).

Finally, regarding the baseline characteristics of the population sample, although it has not been described any influence of ethnic or geographic factors upon IPF prevalence and incidence yet (2), it has been found common features with other studies, such as the men-to-women ratio of 3:1 (1).

11.4 GENERALISABILITY

The study was carried out in 32 centers spread-out all-around Spain, probably providing a representative image of IPF patients of the country. Even more, regardless for the restriction imposed by the third inclusion criteria [“The patients started *de novo* treatment with nintedanib (OFEV®) from 1 January 2016 up to the end of data collection date, according to the approved local summary of product characteristics (SmPC)”], the sample of this study might reproduce all adult IPF patients in Spain.

In reference to a possible worldwide-level inference, caution must be taken since the data source comes from only one country and sample is pretty narrow in reference to the races included (almost 99% Caucasian).

12. OTHER INFORMATION

None.

13. CONCLUSION

This cross-sectional study has drawn the clinical profile of IPF patients treated with nintedanib in Spain. Characteristics such as comorbidities and their treatments are in accordance with those previously reported. Accomplishment of the primary objective has highlighted differences in IPF severity stratification depending on the lung function variable considered. Thus, %FVC has shown that almost 5% of the individuals suffered from severe disease, whereas %DLCO has shown that around one fourth of the population is under this condition. Considering that management of severe-IPF patients is different than the one followed with mild/moderate-IPF patients, it seems that extremely caution should be taken when choosing a stratification based on lung function.

14. REFERENCES

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14.2 UNPUBLISHED REFERENCES

None

15. APPENDICES

The following appendices are provided as stand-alone documents

Appendix 1 NIS Study protocol

Appendix 2 Case Report Form

Appendix 3 Spanish Agency for Medicines and Medical Devices Classification and First Independent Ethics Committee approval

Appendix 4 Statistical Analysis Plan

Appendix 5 Statistical Report

Appendix 6 Coordinating Investigator Signature Page