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Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
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 [redacted] patient). The 98.8% (N=170) of 172 patients were Caucasian, 0.6% (N=1) were [redacted] and 0.6% (N=1) were [redacted].

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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Holder(s):	55216 Ingelheim am Rhein This study is initiated, managed and sponsored by: Boehringer Ingelheim España, S.A C/ Prat de la Riba, 50 08174 Sant Cugat del Vallés (Barcelona)		
Names and affiliations of principal investigators:	[redacted]		