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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:		Nintedanib	
Name of active ingredient:		Active substance: Nintedanib. Anatomical therapeutic chemical (ATC) code: L01EX09	
Report date:	**Study number:**	**Version:**	**Version/Revision Date**
27 Nov 2025	1199-0545	Disclosure Abstract	NA
Title of study:	Observational, multicentre, prospective, real-world post-authorization safety study describing the achievement of nintedanib-associated **DIA**rrhoea control after 12 weeks of follow-up in patients with idiopathic pu**L**monary **FIB**rosis (IPF) and progressive pulmonary fibrosis (other than IPF) in Spain: the DIALFIB study		
Keywords:	Nintedanib, diarrhoea control, IPF, PPF		
Rationale and background:	In the last decade, the treatment of patients with IPF and progressive pulmonary fibrosis (PPFs) have made substantial improvements, based on novel therapies. Nintedanib, one of the two treatments available for IPF and the only treatment available for PPFs, is a tyrosine kinase inhibitor (TKI) that acts by blocking tyrosine kinase enzymes of lung cells receptors, inhibiting the generation of fibrotic tissue [1, 2]. Despite its proven benefits, nintedanib is not exempt of adverse events (AEs), with the most frequent being diarrhoea [3-5]. Indeed, 66.9% to 75.7% of nintedanib-treated patients, present diarrhoea[3-8]. Although most (95%) of nintedanib AEs are categorized as not serious, the high prevalence of diarrhoea and its potential impact on patients health status, often leads to dosage reduction or -in around 13%- to treatment discontinuation, as reported in both randomized clinical trial and real-world-setting studies.[5, 9-12]. In this context and considering the limited treatment alternatives for IPF and PPFs, it is essential to describe the real-world proportion and characteristics of patients who achieve control of nintedanib-associated diarrhoea. This study aimed to describe the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up among patients with IPF and PPFs having a first episode of nintedanib-associated diarrhoea in real world settings in Spain. Study findings were expected to suggest potential alternatives to address this problem and guide future studies aiming to prove the effectiveness of anti-diarrhoea treatments in this population.		
Research question and objectives:	<u>Main research question:</u> Among patients with IPF and progressive pulmonary fibrosis (PPF) (other than IPF) treated with 150 mg bid of nintedanib suffering a first episode of nintedanib-associated diarrhoea in real-world settings in		

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Spain, which is the proportion of patients that achieve diarrhoea control after 12 weeks of follow-up?

Study Objectives:

Primary Objective:

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

Secondary Objectives:

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

Study Outocomes:

Primary Outcome:

1. Achievement of diarrhoea control (yes/no), defined as the passage of less than 3 loose or liquid stools in a 24-hour period (loose or liquid stools defined as stools with a BSFS of 6 or 7 points while being treated with 150 mg bid of nintedanib, at 12-week follow-up.

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	Secondary Outcomes: 1. Absolute change in the proportion of patients taking optimal nintedanib dose (150 mg bid) at 12-week follow-up referent to diarrhoea initiation. 2. Absolute change in BSFS score at week 12 follow-up referent to diarrhoea initiation. 3. Number of stools per day at week 12 follow-up referent to diarrhoea initiation. Change in number of stools per day, as compared to baseline, will be reported. 4. Current body weight (in kilograms) at week 12 follow-up referent to diarrhoea initiation. Change in bodyweight, as compared to baseline, will be reported. 5. Proportion of patients using carob flour for the treatment of nintedanib-associated diarrhoea at any time from diarrhoea initiation to 12-week follow-up. 6. Number of patients per treatment category for nintedanib-associated diarrhoea at diarrhoea initiation 7. Number of patients per treatment category for nintedanib-associated diarrhoea at 12-week follow-up. 8. Occurrence of at least one dose reduction, one dose escalation or permanent withdrawal from the nintedanib dose of 150mg, from diarrhoea initiation to 12-week follow-up.		
Study design and Setting:	This was an observational, non-interventional, multicentre, and prospective, real-world post authorization safety study (PASS), that described the proportion of patients that achieved diarrhoea control after 12 weeks of follow-up in patients with IPF and PPFs who report a first nintedanib-related diarrhoea episode in hospital settings in Spain. It was conducted using primary data collected during routine medical consultations, which was complemented with secondary data extracted from electronic medical records (EMR) and recorded by pulmonologists (or delegates) in an electronic case report form (eCRF). Index date was defined as the date of diarrhoea initiation, and study baseline was defined as the first face-to-face patient visit with their pulmonologist due to a first episode of diarrhoea after the initiation of nintedanib. Baseline visit was performed as close as possible to index date and maximum 4 weeks after index date. Patients were assessed at study baseline and at 3-, 6-, and 12-week follow-up after study baseline.		

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Subjects and study size, including dropouts:	This study included all patients diagnosed with IPF and PPFs who reported a first episode of diarrhoea while being treated with nintedanib optimal dose (150 mg twice per day [bid]). The study duration was from the start of the recruitment period to the last follow-up visit of the last patient, and it was conducted in hospital settings in Spain. Patients were followed from baseline until death, loss of follow-up, or end of study follow-up (12 weeks), whichever came first. Eligible patients were competitively recruited according to the following inclusion and exclusion criteria: **Inclusion criteria** 1. Adults (≥18 years old) at diarrhoea initiation. 2. Ability to consent and to conduct all procedures of the study, as judged by the study investigator, and agreeing to participate providing informed consent at baseline. 3. Diagnosis of IPF or PPFs (other than IPF), as registered in EMR using free text or using disease codes (International Statistical Classification of Diseases and/or Related Health Problems 9th and 10th Revision (ICD-9 and/or ICD-10), at least 1 day before diarrhoea initiation. 4. Being treated with 150 mg bid of nintedanib when initiating diarrhoea symptoms, defined as having a registered nintedanib ATC code (L01EX09) or the molecule/commercial name registered in the EMR, for at least 1 day before diarrhoea initiation. 5. First face to face pulmonologist consultation at the time of recruitment due to a first diarrhoea episode since nintedanib initiation. Diarrhoea defined as the passage of three or more loose or liquid stools in a 24-hour period (loose or liquid stools defined as stools with BSFS of 6 or 7 points). **Exclusion criteria** 1. Patients diagnosed with systemic sclerosis associated interstitial lung disease (SSc-ILD) as registered in EMR using free text or ICD codes (ICD-9 and/or ICD-10). Referent to any time before or at diarrhoea initiation. 2. Participation in any clinical trial including a drug or device. Referent to any time before or at diarrhoea initiation.		

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	3. Participation in any Patient Support Program (PSP) at diarrhoea initiation. 4. Having history of chronic gastrointestinal disorder (e.g., inflammatory bowel disease or the short gut syndrome), pancreatic dysfunction/insufficiency, or colon cancer; due to the likelihood of faecal incontinence. Referent to any time before or at diarrhoea initiation. 5. Having a performance status (PS) ≥3 points on the Eastern Cooperative Oncology Group (ECOG) scale at diarrhoea initiation, due to the likelihood of faecal incontinence. During the recruitment period, 20 patients were considered for the study. After applying inclusion and exclusion criteria, the total number of valid patients was 17. No patients were lost during follow-up period of the study.		
Variables and data sources:	This study used primary data collected by pulmonologists during presential and remote medical contacts, and secondary data obtained from hospital's EMR. The required study information was recorded by pulmonologists (or delegates) in an eCRF. Variables are listed below: **Demographic/clinical characteristics** • Age, years • Sex • Race/ ethnicity • Body mass index (or weight and height), kg/m2 • Smoking status • Pulmonary disease: IPF/PPFs (type of PPF) and date of diagnosis • Comorbidities and date of diagnosis o Arterial hypertension o Diabetes o Gastroesophageal reflux o Coronary heart disease o Sleep apnoea-hypopnea syndrome o Heart disease o Asthma o Chronic bronchitis o Chronic Obstructive Pulmonary Disease		

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- Emphysema
- Lung cancer
- Other relevant comorbidities: names and dates

Health indicators

- Forced Vital Capacity (FVC), in litres
- Diffusing Capacity of Lung for Carbon Monoxide, (% predicted)
- ECOG scale, score

Diarrhoea control achievement, yes/no (<3 loose or liquid stools in a 24-hour period, while being treated with 150 mg bid of nintedanib)

Diarrhoea indicators and body weight

- Number of stools per day
- BSFS score
- Body weight, kilograms

Persistent diarrhoea episode

- Occurrence of persistent diarrhoea episode yes/no
- Number of persistent diarrhoea episodes

Duration of first nintedanib-associated diarrhoea episode, days

Time from nintedanib initiation to the first diarrhoea episode, days

Nintedanib use

- Optimal dose
- Dose reduction
- Drug withdrawal (permanent/ temporal)
- Dose escalation

Concomitant treatment to nintedanib (excluding treatment of nintedanib-associated diarrhoea)

- Receiving concomitant treatment, yes/no
- Drug name, start date

Clinical management of nintedanib-associated diarrhoea

- Receiving treatment for nintedanib-associated diarrhoea, yes/no
- Type of pharmacological treatment (treatment names and start and end dates) (e.g., loperamide)

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	• Type of non-pharmacological treatment (treatment names and start and end dates) (e.g, carob flour, zinc, probiotics, other dietary interventions, hydration) • Treatment combinations **Loss of follow-up, yes/no** **Adverse Drug Reactions**		
Statistical methods:	Descriptive statistics are presented as absolute and relative frequencies for categorical variables; and mean, standard deviation, median, 25 and 75 quartiles, and minimum, and maximum values for continuous variables. The comparisons of variables were performed according to the distribution of the variable. Normally distributed values were confirmed using the Shapiro Wilk test. The follow-up vs. baseline for continuous variables was analysed using Student's paired t-test. For non-normal distributed values, Wilcoxon signed-rank test was used. Categorical variables were tested with Fisher's exact test when low frequencies, or with Chi-Squared test. P-values were provided as descriptive representations of the data for the analysis of different subgroups and different timepoints if it is required. Interim analysis was not conducted.		
Results:	During the recruitment period, 18 patients were included in the study. One patient was subsequently excluded due to not fulfilling the eligibility criteria, resulting in a final analysed population of 17 patients. At baseline, the mean (SD) age of the included population (n=18) was 70.28 (6.88) years, and 14 patients (77.78%) were male. Most patients were White 16 (88.89%), followed by Latino 1 (5.56%) and Black 1 (5.56%). Mean (SD) body mass index (BMI) was 28.97 (5.67) kg/m² and mean (SD) body weight was 80.84 (16.68) kg. Regarding smoking status, 13 (72.22%) were ex-smokers, 4 (22.22%) non-smokers, and 1 (5.56%) smoker. 17 patients were finally eligible and finished the study. Among these eligible patients, the most common comorbidities were arterial hypertension (suffered by 47.06% of patients), sleep apnoea (29.41%), emphysema (29.41%), diabetes (23.53%) and coronary heart disease (23.53%). Of the 17 eligible patients, 70.59 % achieved diarrhoea control while taking a nintedanib dose of 150 mg twice daily (bid) at the 12-week follow-up. 76.47% of patients were taking the optimal nintedanib dose		

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	at the 12-week follow-up. BSFS score in the 12-week follow-up, as compared to the baseline visit, presented a mean (SD) difference of -1.76 (1.60). During this period, mean (SD) change for number of stools was -2.09 (1.27) stools per day. Mean body weight in kilograms presented a mean

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	(SD) difference of -0.66 (1.93), and a mean (SD) relative change of -0.85 (2.42). Regarding diarrhoea treatment, at diarrhoea initiation 9 (75.00%) patients were under only non-pharmacological treatment and 3 (25.00%) were under both pharmacological and non-pharmacological treatment. After the 12 weeks follow-up 1 (7.14%) patient was only under pharmacological treatment, 11 (78.57%) patients were only under non-pharmacological treatment, and 2 (14.29%) patients were under combined pharmacological and non-pharmacological treatment. 88.24% used carob flour anytime from diarrhoea initiation to 12-week follow-up. Carob flour was most combined with loperamide and other dietary supplementary, and 52.94% of patients experienced at least one persistent diarrhoea episode for, at least, 14 days between diarrhoea initiation and the end of the follow-up. Mean time from nintedanib initiation to diarrhoea appearance was 8.73 months, and mean duration of these episodes was 33.06 days. 23.53% of patients had to interrupt their nintedanib treatment at least once during the follow-up. During the whole study period, 7 (41.14%) patients changed their nintedanib dose, 5 (29.41%) of them due to diarrhoea. 4 (57.14%) dose reductions, 4 (57.14%) dose escalations and 4 (57.14%) drug withdrawals took place. None of the patients reported definitive withdrawal. One patient included in the study cohort reported one Adverse Event (AE) at 6 weeks follow-up visit. The AEs was related to gastrointestinal motility and defaecation conditions, more specifically diarrhoea, and it was considered non serious. Medication (OFEV) was interrupted for the patient's recovery, and, after reintroducing medication, symptoms did not reappear. Focusing on all recorded patients, a total of 4 AEs were suffered by 2 patients during the study period. Of those 2 patients, one was finally excluded. AEs were related to gastrointestinal motility and defaecation conditions, more specifically diarrhoea, and they were considered non serious. In one patient, medication (OFEV) was interrupted 3 times and later reintroduced 2 times. After reintroducing medication, symptoms reappeared in this patient. No serious adverse events or deaths occurred over the course of the study. 70.59% of patients receiving the optimal dose of nintedanib achieved diarrhoea control. The BSFS score at 12 weeks was 4.71 ± 1.40. The			

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	change between baseline and week 12 was −1.76 ± 1.60. During the study, there were no permanent discontinuations of treatment.		
Discussion:	Despite the small sample size, the results of this study align with previous research, and they suggest that most patients with IPF and other PPFs achieved diarrhoea control after 12 weeks of follow-up after receiving nintedanib, with most patients continuing to receive the optimal nintedanib dose. At the same time, carob flour was frequently used as a non-pharmacological approach for diarrhoea management, with observed improvements in stool production, number and consistency of stools, and BSFS score. With no adverse events reported, the use of this product is an excellent option to treat and control diarrhoea complications derived from the use of antifibrotic drugs like nintedanib. Further studies with larger populations are warranted to confirm these findings and evaluate carob flour as a supportive measure.		
Marketing Authorisation Holder(s):	Boehringer Ingelheim International GmbH Binger Straße 173 55216 Ingelheim am Rhein, Germany [redacted]		
Names and affiliations of principal investigators:	Coordinator investigator: - [redacted] Principal investigators who recruited patients: - [redacted]		

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