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Study number: 1199-0449

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Ofev®			
Name of active ingredient: L01XE31 Nintedanib			
Report date: 13 Mar 2025	Study number: 1199-0449	Version/Revision: 1.0	Version/Revision date: Not applicable
Title of study:	Prospective observational investigation of possible correlations between change in FVC and change in cough or dyspnea scores using the living with pulmonary fibrosis questionnaire (L-PF) between baseline and after approximately 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype.		
Brief title of study:	INREAL – Nintedanib for changes in dyspnea and cough in patients suffering from chronic fibrosing interstitial lung disease (ILD) with a progressive phenotype in everyday clinical practice: a real -world evaluation		
Keywords:	Chronic fibrosing ILD with a progressive phenotype; nintedanib; lung function; symptom burden; L-PF dyspnea and cough symptom scores		
Rationale and background:	"Chronic fibrosing Interstitial Lung Disease (ILD) with a progressive phenotype" includes the most common ILD Idiopathic Pulmonary Fibrosis (IPF) and other ILDs like hypersensitivity pneumonitis (HP), rheumatoid arthritis-associated ILD (RA-ILD) and Systemic Sclerosis-ILD (SSc-ILD). Progressive fibrosis leads to worsening lung function, dyspnea, cough, increased mortality, and reduced quality of life. Nintedanib has been shown in clinical trials (TOMORROW, INPULSIS-1 and -2) to be effective for IPF, slowing lung function decline with manageable side effects. Real-world data support these findings. The INBUILD trial indicated that nintedanib also slowed the Forced Vital Capacity (FVC) decline in patients with various progressive fibrosing ILDs, not just IPF. This study investigates nintedanib’s effects on patient-reported outcomes (PROs) like dyspnea and cough in chronic ILD patients (excluding IPF) over 52 weeks in a real-world setting. Using the "Living with Pulmonary Fibrosis" (L-PF) questionnaire, symptoms (dyspnea, cough, fatigue) and impacts on patients' lives were assessed. Changes in FVC were correlated with changes in symptom scores to better understand nintedanib's impact on FVC decline and symptomatic burden.		
Research question and objectives:	The study hypothesis was that in a one-year observational study a correlation can be found between changes in lung function measured by FVC and the changes in the scores for dyspnea and cough of the L-PF questionnaire in ILD patients. <u>Primary objective:</u> • To investigate the correlation between changes from baseline to 52 weeks in FVC [% pred.] and changes from baseline to 52 weeks in		

	dyspnea score [points] or cough score [points] as measured with the L-PF questionnaire over 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype (excluding IPF). <u>Primary outcomes:</u> - Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in dyspnea symptom score - Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in cough symptom score <u>Secondary objectives:</u> - To investigate the correlation between changes from baseline to 52 weeks in FVC [ml] and changes from baseline to 52 weeks in dyspnea score [points] or cough score [points] as measured with the L-PF questionnaire over 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype (excluding IPF). - To assess the absolute change from baseline to 52 weeks in L-PF cough and dyspnea scores. <u>Secondary outcomes:</u> - Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in dyspnea symptom score - Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in cough symptom score - Absolute change from baseline to week 52 in L-PF cough symptom score - Absolute change from baseline to week 52 in L-PF dyspnea symptom score
Study design:	Observational study according to §4, section 23 and §67, section 6 German Medicines Act (NIS) based on newly collected data.
Setting:	The study was submitted to the ethics committee on 21-Dec-2020. Final approval was on 23-Feb-2021. Data collection on the effect of nintedanib in patients with chronic fibrosing ILD with progressive phenotype started in June 2021 and was finished in April 2024. A total of 21 study sites were initiated throughout Germany. Of these, specialized physicians experienced in treating ILD patients (e.g. pulmonologists and rheumatologists) at 17 sites recruited 108 patients. After two prolongations due to slow recruitment, recruitment ended on 31-Mar-2023.
Subjects and study size, including dropouts:	<u>Inclusion criteria</u> - Adults ≥ 18 years at Visit 1. - Subjects must be contractually capable and mentally able to understand and follow the instructions of the study personnel. - Physician's diagnosis of chronic fibrosing ILD with a progressive phenotype, except IPF.

	• Treatment with nintedanib in INREAL will be the first and only prescription of any antifibrotic treatment for each individual patient within this observational study after a physician's decision being made for this treatment option earlier. • Outpatients not currently hospitalized with a life expectancy >12 months per investigator's assessment. • Written informed consent prior to study participation. • Current FVC measurement (taken within the last 3 months) available in the patient file. • Women of childbearing potential must take appropriate precautions against getting pregnant during the intake of nintedanib. <u>Exclusion criteria</u> • Patients with contraindications according to SmPC. • Prior use of any antifibrotic treatment. • Lack of informed consent. • Pregnant or lactating females. • Any physician diagnosed exacerbation of ILD in the patient's history file, irrespective of time since event. • Current diagnosis of lung cancer. • Respiratory failure (pH < 7,35 and/ or respiratory rate > 30/min) in the patient's history. • Participation in a parallel interventional clinical trial. • Patients being spouse or lateral relatives to the second degree or economically dependent from the investigator. A total of 108 patients were registered for the study, with 102 receiving nintedanib treatment. Of these, 71 patients completed the study regularly, 10 died, 7 were lost to follow-up, 3 withdrew, and 11 terminated the study early for other reasons.
Variables and data sources:	The following parameters were collected and assessed at visits 1 to 5, as applicable: • Patient demographics (age, sex, height, weight) • Smoking history, current status (current smokers, former smokers, and never smokers) and pack-years • History of ILD, including ILD entity and HRCT pattern (where available in patient documentation) • current DL_{CO} measures (where available in patient documentation) • Concomitant diseases • Previous ILD therapies in the 6 weeks before visit 1 • Current ILD related or other relevant concomitant medication • FVC (mL and % pred.; if available in patient data) • Severity of disease as per the treating physician's estimation (if available in patient data) • L-PF questionnaire, completed by patient • Safety: ADRs (serious and non-serious), fatal AEs, pregnancies during the study • Rationale for treatment discontinuation (if applicable)

	• Intention to continue or discontinue treatment with nintedanib (Ofev®) after the study (yes/no) • Further treatment options yes/no, as applicable Medical records collected through routine clinical care were used to assess the inclusion/exclusion criteria, patient demographics, smoking history, collection of previous ILD medication, concomitant diseases, concomitant medication, and health data of the patient during the observation. The L-PF questionnaire was filled out on paper at visits V1 to V5, as applicable. No further data sources were needed for statistical analysis. Due to the observational nature of the study, all analyses were exploratory. No weighting was applied to either of the co-primary endpoints. For the analysis of the primary and secondary outcomes, Pearson measures of correlation along with 95% two-sided confidence intervals and the two-sided p-values were provided. Absolute changes from baseline in L-PF dyspnea and cough scores between week 52 and baseline were analysed using a Restricted Maximum Likelihood (REML) estimator for Mixed Model for Repeated Measures (MMRM) approach. Analyses included the fixed, categorical effect of visit, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured (co)variance structure was used to model the within-patient measurements. No interim analysis was performed.
Results:	The study population, consisting of 102 treated patients, had a mean age of 70.47 ± 10.74 years. The study population included a higher proportion of males (62.75%). Race and ethnicity were not collected. Approximately half of the participants were either former (45.10%) or current (3.92%) smokers. Most patients were diagnosed with autoimmune disease associated ILDs (44.12%), followed by IIPs (32.35%), exposure related ILDs (19.61%), and sarcoidosis (3.92%). At baseline, the mean FVC was $65.18 \pm 18.86\%$ pred. and 2296.37 ± 769.77 ml. After 52 weeks of nintedanib treatment, mean FVC was $65.67 \pm 19.62\%$ pred. and 2304.79 ± 710.73 ml. The mean dyspnea symptom score was 24.71 ± 18.56 at baseline and after 52 weeks of nintedanib treatment, the score was 27.32 ± 21.67. The mean cough symptom score was 37.46 ± 25.67 at baseline and 36.85 ± 28.59 after 52 weeks of nintedanib treatment. Due to missing patient questionnaires or other necessary variables for 64 out of all 102 patients, the primary outcome was analyzed for a total of 38 patients. For the primary outcome, the correlation between change in FVC [% pred.] and change in dyspnea symptom score, the Pearson correlation coefficient was -0.26 and the p-value was 0.12 (95% CI -0.53 to 0.07). For the correlation between change in FVC [% predicted] and change in cough symptom score, the Pearson correlation coefficient was -0.11 and the p-value was 0.51 (95% CI -0.41 to 0.22). For the secondary outcome, the correlation between the change in FVC [ml] and change in dyspnea symptom score, the Pearson correlation coefficient was -0.29 and the p-value was 0.08 (95% CI -0.56 to 0.03). For the correlation between change in FVC [ml] and change in cough symptom score, the Pearson correlation coefficient was -0.16 and the p-value was 0.35 (95% CI -0.45 to 0.17). Absolute change in dyspnea symptom score from

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	baseline to week 52 was 6.75 ± 18.51, and in cough symptom score it was 2.50 ± 24.04. Throughout the study, 69 patients (67.65%) experienced 139 TEAEs. Overall, 24 STEAEs were reported in 16 patients (15.69%), 91 TEADRs in 53 patients (51.96%), 3 STEADRs in 3 patients (2.94%), and 4 TEASIs in 3 patients (2.94%). There were 10 fatal STEAEs among 8 patients (7.84%).
Discussion:	INREAL provides valuable insights into the real-world use of antifibrotic therapy in patients with chronic fibrosing ILDs exhibiting a progressive phenotype. The absence of a control group and the small sample size are challenges, but the real-world setting of INREAL captures the diverse patient population typically seen in daily clinical practice. The primary outcome results indicate no significant correlation between changes in FVC [% predicted] and changes in dyspnea or cough symptom scores. However, the analysis of L-PF symptom scores, particularly dyspnea and cough, shows that quality of life stays relatively stable over a 52 weeklong treatment with nintedanib.
Marketing Authorisation Holder(s):	[REDACTED]
Names and affiliations of principal investigators:	[REDACTED]