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1. ABSTRACT

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Name of finished medicinal product: Ofev®			
Name of active ingredient: L01XE31 (Nintedanib)			
Report date: 5 Dec 2023	**Study number:** 1199-0355	**Version/Revision:** 1.0	**Version/Revision date:** N/A
Title of study:	Investigating Trends in Quality of Life in Patients with IPF Under Treatment with Nintedanib (QUALIFY IPF)		
Keywords:	Idiopathic Pulmonary Fibrosis (IPF), real-life, nintedanib, health-related quality of life (HRQoL), St. George's Respiratory Questionnaire		
Rationale and background:	IPF is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, limited to the lungs. It is characterized by progressive worsening of dyspnoea and lung function and is associated with a poor prognosis. IPF predominantly presents in older individuals, with a preponderance in men and previous or current smokers. Patients present with unexplained chronic exertional dyspnoea, and commonly with cough, bibasilar inspiratory crackles, and finger clubbing. At the time of the design of this study, the diagnosis of the disease was based on the 2011 American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guidelines, requiring exclusion of identifiable causes of interstitial lung disease (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity) as well as identification of a pattern of usual interstitial pneumonia either on high-resolution computed tomography (HRCT) or on surgical lung biopsy. The natural history of IPF is highly variable and the course of the disease is unpredictable for a given patient at the time of diagnosis, with some patients progressing slowly, others rapidly, and some patients experiencing acute exacerbations that are associated with increased morbidity and mortality.		

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Up to 2011, there was no effective pharmacological treatment for IPF other than lung transplantation, which was considered the only survival-improving intervention. Since then, two agents, pirfenidone and nintedanib, have been introduced as therapeutic options following the results of Phase III randomized clinical trials (RCTs) showing that these agents reduce the decline in lung function in comparison to placebo.

Nintedanib is a multi-target tyrosine kinase inhibitor with activity against vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) receptors, that are implicated in the pathogenesis of IPF. In its pivotal RCTs – Phase II TOMORROW study and the two replicate Phase III studies INPULSIS-1 and INPULSIS-2 – nintedanib at a dose of 150 mg twice daily slowed disease progression by reducing the annual rate of decline in forced vital capacity (FVC) in patients with IPF and mild or moderate lung function impairment.

Due to the rarity of IPF, there are very limited data regarding the patients' clinical characteristics, the natural course of the disease and the medical treatment these patients receive. In a call for action on an IPF registry by Wilson in 2008, it was noted that improved survival from this disease is dependent on better understanding of the epidemiology of the disease, its diagnostic spectrum and an analysis of outcomes from emerging therapies at a significant level.

Indeed, a significant achievement towards the above goal is the establishment of patient registries, with numerous national IPF registries already established in countries around the world. The ongoing experience

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with these registries has indeed provided valuable insights to guide clinical management of IPF in the "real-world" adjusted to local needs as well as important information towards the development of a global registry.

With regards to the Greek population, very few data are available regarding the use of nintedanib in cohorts of patients with IPF either pre-treated or treatment-naïve, also in terms of Patient-Reported Outcomes (PROs). A recently launched registry, INDULGE-IPF (manuscript under submission), is expected to provide essential data regarding the natural course of IPF and the treatment of the disease – including the use of nintedanib – in the Greek population.

In a chronic disease such as IPF, the goal of pharmacological treatments should not only be survival prolongation, but also delay in the progression of the disease and on the clinical deterioration of patients, i.e., delay in worsening of symptoms and QoL. Nevertheless, an effective treatment in such a chronic disease may lead to long-term exposure, and thus to cumulative toxicity that can also adversely affect patients' QoL.

In IPF, there is a paucity of well-validated PRO measures. In the pooled analysis of nintedanib randomized trials in IPF, the use of St. George's Respiratory Questionnaire (SGRQ) as a measurement of HRQoL provided evidence for a modest effect of nintedanib on the delay of clinical deterioration of patients. In addition, a German IPF registry (INSIGHTS-IPF) has published results for PROs in enrolled patients, showing IPF patients under real-life conditions have lower HRQoL compared to those in clinical studies. In the Greek population though, analogous results regarding

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	the effect of nintedanib on the SGRQ as well as other PRO measures are still lacking.		
Research question and objectives:	Thus, the aim of this non-interventional study (NIS) based on newly collected data was to collect data on various important PROs in patients with IPF that could provide useful insights about HRQoL in patients treated with nintedanib over 52 weeks in the real-world setting in Greece. To this end, this study utilized PROs in a cohort of newly diagnosed IPF patients that had recently started treatment with nintedanib in order to provide relevant information regarding IPF-related symptoms and their impact on several aspects of everyday life activities including psychological consequences. Periodical completion of PROs allowed to record the evolution of IPF symptoms and their effects on HRQoL. Finally, adherence to treatment was recorded. Patients also reported on very specific symptoms (e.g., cough, dyspnoea) and their functional impact, which are concepts proximal to patients' experience with the disease and treatment. **Primary objective** • To evaluate changes from baseline of HRQoL for IPF patients treated in current clinical practice in Greece with nintedanib at the timepoints of 3, 6, 9 and 12 months over a 52-week period, via the SGRQ. **Secondary objectives** • To assess changes from baseline in dyspnoea and cough in IPF patients treated with nintedanib in current clinical practice in Greece at the timepoints of 3, 6, 9 and 12 months over a 52-week		

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	period, via specific questionnaires, such as the modified Medical Research Council (mMRC) scale and Cough - Visual Analogue Scale (Cough - VAS), respectively. • To estimate the adherence to nintedanib treatment in current clinical practice at the timepoints of 3, 6, 9 and 12 months over a 52-week period via the Simplified Medication Adherence Questionnaire (SMAQ) [adapted for the treatment of IPF]. • To measure anxiety in IPF patients treated with nintedanib in current clinical practice in Greece at the timepoints of baseline, 3, 6, 9 and 12 months over a 52-week period via the General Anxiety Disorder-7 (GAD-7) questionnaire. • To estimate the use of Long-Term Oxygen Treatment (LTOT) among IPF patients under treatment with nintedanib in current clinical practice in Greece at the timepoints of baseline, 3, 6, 9 and 12 months over a 52-week period.
Study design:	QUALIFY IPF was a national, multicentre, non-interventional, prospective cohort study in newly diagnosed IPF patients (initial IPF diagnosis no more than 3 months prior to enrolment) according to 2011 ATS/ERS/JRS/ALAT guidelines initiating treatment with nintedanib in reference centres across Greece and being followed over a period of 52 weeks.
Setting:	Data of 180 newly diagnosed IPF patients enrolled from 10 University Pulmonology Clinics and Reference Centres of the Public Hospital Setting across Greece were collected. Hospital Pulmonary Clinics acted as coordinating sites of the study. All included sites were reference centres for IPF, both in Athens and the rest of Greece, so that patients enrolled would constitute a representative population of IPF patients in Greece. Each

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investigator was requested to consecutively enrol 10-12 newly diagnosed IPF patients (initial IPF diagnosis no more than 3 months prior to enrolment) according to 2011 ATS/ERS/JRS/ALAT guidelines who were initiating treatment with nintedanib as per his/her discretion and the routine clinical practice in the corresponding site.

The study was scheduled to run for 4 years in total, i.e., 3 years of recruitment and 1 year of follow-up. The study collected data from five visits: at baseline (at treatment initiation or within one week after treatment initiation) and at 4 standard clinical visits performed during the follow-up according to the clinical practice scheduled approximately at: 3 months (± 1 month), 6 months (± 1 month), 9 months (± 1 month), 12 months (± 1 month) until the end of participation in the study. Patients that would permanently discontinue nintedanib treatment/withdraw from the study for any reason [e.g., due to Adverse Event (AE), consent withdrawal, lost to follow-up] prior to the follow-up period completion, would no longer be followed within the context of the study and the visit that nintedanib/study discontinuation had been recorded would be considered as their final, end of study visit.

Patients were enrolled from 28 February 2019 to 28 February 2022. In the context of this study, participating physicians followed each enrolled patient for a planned observation period of 12 months, starting from the date of the baseline visit and ending at the earliest of treatment discontinuation, withdrawal of consent, physician's decision to withdraw the patient, 12-month follow-up period completion, death or when any other discontinuation criterion would be met.

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Subjects and study size, including dropouts:	Patients were considered eligible to participate in the study, if they were fulfilling all the inclusion criteria and none of the exclusion criteria: ***Inclusion criteria*** • Patients ≥40 years of age. • Patients that had signed Informed Consent Form (ICF). • Treatment-naive patients with an initial IPF diagnosis no more than 3 months prior to enrolment according to 2011 ATS/ERS/JRS/ALAT guidelines who were initiating treatment with nintedanib (as monotherapy for IPF), the latest on the enrolment day or had initiated treatment with nintedanib (as monotherapy for IPF) within the past 7 days prior to enrolment. • Patients for whom the decision to prescribe therapy with nintedanib according to the locally approved product's Summary of Product Characteristics (SmPC) had already been taken prior to their enrolment in the study and was clearly separated from the physician's decision to include the patient in the current study. • Patients that were able to read, understand and complete the study-specific questionnaires. ***Exclusion criteria*** • Treatment with nintedanib for more than 7 days prior to study enrolment. • Patients receiving a combination therapy of nintedanib & pirfenidone for IPF. • Patients that met any of the contraindications to the administration of the study drug nintedanib according to the approved SmPC.		

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	• Prior treatment with pirfenidone or other treatment for IPF. • Participation in an interventional study. • Patients receiving treatment with any investigational drug/device/intervention or had received any investigational product within 1 month or 5 half-lives of the investigational agent (whichever is longer) before the initiation of therapy with nintedanib. Thus, a total of 180 eligible patients were enrolled in the QUALIFY IPF study from 28 February 2019 to 28 February 2022, of which 149 (82.78%) completed the planned observation period and 31 (17.22%) discontinued from the study. Reasons for discontinuation included AE occurrence (19 patients; 10.56%), lost to follow-up (3 patients; 1.67%), treatment discontinuation (1 patient; 0.56%) and patient's decision/ICF withdrawal (1 patient; 0.56%). All enrolled patients received at least one dose of nintedanib and thus were included in the primary statistical analysis comprising the Treated Set (TS).
Variables and data sources:	The study mainly included the collection of new data recorded through an existing web-based database (electronic case report form; eCRF). Data were collected by the study doctors as they occurred according to standard clinical practice in the approximate visiting schedule indicated above. Patients' source (primary) data related to their medical and IPF history were derived by the investigators from their medical records and were documented in the relevant eCRF section. Data regarding treatment modifications, concomitant treatments, study-related routine clinical assessments, adverse events (ADRs) and survival status were also collected. PROs implemented in this study, including SGRQ, mMRC and Cough-VAS

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were completed by the patient either by himself/herself or in collaboration with the participating physician or the study nurse, if available.

At baseline, a relevant patient history was recorded. Moreover, the current status of IPF patients was recorded in terms of

- Basic (socio-)demographic characteristics
- Anthropometric characteristics (weight, height)
- Vital signs and physical examination
- Potential IPF risk factors
- Comorbidities and concomitant medications
- Methods used in IPF diagnosis [including High-Resolution Computed Tomography (HRCT), surgical lung biopsy (SLB) and bronchoalveolar lavage (BAL), if available]
- IPF symptoms
- Nintedanib treatment (start date, daily dose)
- Functional assessment [including lung function test, and/or exercise capacity test (6-minute walking test; 6-MWT) if available]
- PROs (SGRQ, mMRC Score, Cough - VAS, GAD-7)
- LTOT

During the follow-up visits (prospectively up until a maximum of 12 months from baseline) at 3 months (± 1 month), 6 months (± 1 month), 9 months (± 1 month) and 12 months (± 1 month), the following variables were recorded:

- Anthropometric characteristics (body weight)
- Vital signs and physical examination
- Nintedanib treatment (stop date, restart date in case of temporary discontinuation, daily dose)

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- PROs (SGRQ, mMRC Score, Cough - VAS, GAD-7)
- LTOT
- Changes in concomitant medications
- Survival status

Primary outcome:

The mean change from baseline in HRQoL (with reference to SGRQ score, both total score and score in each of the SGRQ domains) of patients under treatment with nintedanib, as assessed by the changes in SGRQ score at the timepoints of 3, 6, 9 and 12 months over the 52-week follow-up period.

Secondary outcomes:

- The mean change from baseline to 3-, 6-, 9- and 12-month follow-up period of dyspnoea burden, as measured via changes in the mMRC score
- The mean change from baseline to 3-, 6-, 9- and 12-month follow-up period of cough burden, as measured via changes in the Cough - VAS
- The percentage of adhered patients to nintedanib treatment at the timepoints of 3, 6, 9 and 12 months over the 52-week follow-up period, as measured via the SMAQ questionnaire (adapted for the treatment of IPF)
- The mean change from baseline to 3-, 6-, 9- and 12-months follow-up period of anxiety in patients treated with nintedanib, as measured via the GAD-7 questionnaire
- The percentage of patients using LTOT at the timepoints of 3, 6, 9 and 12 months over the 52-week follow up period

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Results:	Among a total of 180 patients (TS), the majority were males (75.56%), and the mean ± standard deviation (SD) age at baseline was 72.96 ± 7.829 years; all patients were White/Caucasian. Patients had a mean (SD) Body Mass Index (BMI) of 29.01 ± 4.437 kg/m^2. A smoking history was reported by 130/180 [72.23%] patients (111/180 [61.67%] being former smokers and only 19/180 [10.56%] being current smokers) accounting for a mean ± SD of 44.29 ± 29.954 pack-years. Exposure to environmental or occupational risk factors was only reported by 15/180 (8.33%) and 35/180 (19.44%) patients, respectively. Gastroesophageal reflux (GERD) was also reported as a risk factor in 27/180 (15.00%) patients. Alcohol and drug abuse as well as exposure to microbial agents was not reported except for 1 patient reporting alcohol abuse. Finally, 12/180 (6.67%) patients reported a family history of IPF. The first symptoms indicative of IPF had occurred 21.50 weeks (median; range 0-490.1) prior to baseline, while the median time since initial diagnosis was 6 weeks (range 0-13.1). Diagnosis for the vast majority of patients (97.78%) was based on HRCT, which revealed the following patterns, according to the ATS/ERS 2011 criteria: Usual Interstitial Pneumonia (UIP) pattern in 77.22% of patients, possible UIP in 18.89%, and inconsistent UIP pattern in 1.67%. SLB was only performed in 3 (1.67%) patients, revealing possible UIP in 1 patient (0.56%) and probable UIP in the other 2 patients (1.11%). BAL was also performed in 68 (37.78%) patients. Most recent BAL analysis revealed a median absolute cell count/concentration of 200 × 10^3 (interquartile range [IQR] 144 × 10^3 -506 × 10^3) cells/mL and the following differential count: a median of 5.70 (IQR 3.00-10.08)% lymphocytes, 83.05 (64.00-91.06)% macrophages, 1.40		

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(0.50-3.00)% eosinophils, and 4.55 (2.68-13.25)% granulocytes as well as a median $CD4^+/CD8^+$ of 1.68 (IQR 0.69-3.00).

Among symptoms and signs indicative of IPF present at baseline, dyspnoea (81.11%), cough (71.11%) as well as bibasilar crackles (68.89%) were the most frequently reported.

The mean FVC ± SD at baseline was 79.52 ± 20.199% predicted and the mean diffusing capacity of the lung for carbon monoxide (DL_{CO}) ± SD was 49.34 ± 16.61% predicted (Hb-corrected). Most patients had an FVC ≥70% predicted (122/176; 69.32% of patients; 4 with no data available) and an DL_{CO} ≥40% predicted (Hb-corrected) (123/169; 72.78% of patients; 11 patients with data not available) indicating mild disease. Accordingly, the highest proportion of patients were at gender-age-physiology (GAP) stage II (77/175; 44.00%) followed by GAP stage I (75/175; 42.86%) and GAP stage III (23/175; 13.14%). A 6-min walking test was only performed by 87 patients, with a median walking distance of 340 (IQR 300.00-435.00) metres reported.

Most patients (80.00%) had at least one clinical diagnosis other than IPF [a median of 2 (IQR 1.0-2.0) comorbidities] at baseline. Among the comorbidities of interest, arterial hypertension was the most frequently reported (46.67%), while among other comorbidities reported, 34.44% of patients had dyslipidaemia and 19.44% had diabetes mellitus.

In 97.78% of patients, treatment with nintedanib was initiated using the recommended dose, i.e., 150 mg twice daily, while only 4 patients (2.22%) initiated treatment with a lower dose of nintedanib, i.e., 100 mg twice daily;

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1 patient due to hypertensive cardiopathy, 1 patient due to a glomerular filtrate rate (GFR) of 34 ml/min and 2 patients with no reason recorded. Overall, the median (IQR) exposure to nintedanib at any dose during this study was 366 (343-379) days; 82.22% and 52.78% of patients were exposed to nintedanib for ≥48 and ≥52 cumulative weeks, respectively. Moreover, 80.56% of patients were also taking at least one concomitant medication other than nintedanib, most commonly medications for cardiovascular conditions (109 patients; 60.56%) and medications for alimentary tract and metabolism disorders (66 patients; 36.67%).

Analysis of primary outcome

Based on observed data, the mean ± SD SGRQ total score at baseline was 32.93 ± 19.32, indicating moderate impairment relative to the population norms. Patients had the greatest impairment in the activity domain (48.19 ± 22.95656) followed by the symptom domain (32.09 ± 21.089) and finally the psychosocial impact domain (24.01 ± 20.48787).

Based on an MMRM approach (primary analysis), adjusted least squares (LS) mean SGRQ total score following treatment with nintedanib increased (i.e., deteriorated) from baseline by 2.08 (95% Confidence Interval [CI]: -2.15, 6.31), by 3.55 (95% CI: -0.71, 7.8), by 4.64 (95% CI: 0.36, 8.92) and by 6.00 (95% CI: 1.72, 10.28) points at 3, 6, 9 and 12 months, respectively, all changes not exceeding the 7-point minimal important difference (MID).

In the symptoms domain, the adjusted LS mean SGRQ score following treatment with nintedanib decreased (i.e., improved) non-statistically significant from baseline by 2.31 (95% CI: -1.27, 5.89), by 1.28 (95% CI: -

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2.33, 4.9), by 1.07 (95% CI: -2.57, 4.72) and by 1.03 (95% CI: -2.62, 4.67) points at 3, 6, 9 and 12 months, respectively, with changes not exceeding the 8-point MID.

In the activity domain, the adjusted LS mean SGRQ score following treatment with nintedanib increased (i.e., deteriorated) non-statistically significant from baseline by 3.37 (95% CI: -1.15, 7.89), by 4.18 (95% CI: -0.37, 8.73), by 5.36 (95% CI: 0.78, 9.94) and by 6.19 (95% CI: 1.61, 10.77) points at 3, 6, 9 and 12 months, respectively, with changes at 9 and 12 months exceeding the 5-point MID.

Finally, the adjusted LS mean SGRQ score in the psychosocial impact domain following treatment with nintedanib increased (i.e., deteriorated) non-statistically significant from baseline by 2.88 (95% CI: -2.1, 7.85), by 4.76 (95% CI: -0.25, 9.77), by 6.09 (95% CI: 1.05, 11.13) and by 8.17 (95% CI: 3.13, 13.22) points at 3, 6, 9 and 12 months, respectively, with change at month 12 exceeding the 7-point MID.

Analysis of secondary outcomes

Patients' dyspnoea burden according to the mMRC

With regards to dyspnoea, of the patients reporting symptoms of breathlessness at baseline (85%), the majority were classified as mMRC grade 1 (45.56%), followed by grade 2 (22.22%), grade 3 (11.11%), while only 6.11% had grade 4. Overall, no apparent shift towards a better condition in terms of breathlessness was observed following treatment with nintedanib for 3, 6, 9 or 12 months.

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Accordingly, based on observed data, mean ± SD mMRC score at baseline was 1.48 ± 1.070, while following treatment with nintedanib for 3, 6, 9 and 12 months, the adjusted LS mean mMRC score (MMRM approach) increased (deteriorated) from baseline by 0.30 (95% CI: 0.09, 0.51), by 0.31 (95% CI: 0.10, 0.51), by 0.40 (95% CI: 0.19, 0.61) and by 0.39 (95% CI: 0.18, 0.60), respectively, indicating a minimal increase on the impact of dyspnoea on daily activities, although a minimally clinically important difference (MCID) has not be defined in IPF.

Patients' cough burden according to the Cough VAS

Based on observed data, mean ± SD Cough VAS score at baseline was 28.94 ± 22.793 indicating a mild cough attributed to IPF. Based on an MMRM approach, at 3, 6, 9 and 12 months, the adjusted LS mean Cough VAS score decreased (improved) from baseline by 0.72 (95% CI: -3.42, 4.87), by 3.73 (95% CI: -0.45, 7.92), by 2.13 (95% CI: -2.09, 6.36) and by 1.25 (95% CI: -2.98, 5.48), respectively, following treatment with nintedanib, indicating a reduction in the impact of cough on daily activities (no MID has been reported in IPF).

Patients' anxiety according to GAD-7

At baseline, the majority of patients (62.78%) had minimal anxiety, 23.89% had mild, and only 7.78% and 5.56% had moderate and severe anxiety, respectively, based on their GAD-7 score. Accordingly, mean ± SD GAD-7 score at baseline was 4.38 ± 4.851 (observed data) indicating minimal anxiety, while based on an MMRM approach (primary analysis), the adjusted LS mean GAD-7 score increased (i.e., worsened) from baseline by 0.09 (95% CI: -1.19, 1.38), by 0.48 (95% CI: -0.81, 1.77), by 0.77 (95% CI:

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	-0.53, 2.07) and by 0.97 (95% CI: -0.33, 2.26) following treatment with nintedanib for 3, 6, 9 and 12 months, respectively. ***Rate of adherence to nintedanib according to the SMAQ up to 12 months of treatment*** Assessment of treatment adherence using the SMAQ showed that 70.75%, 74.13%, 75.18% and 76.81% of the patients were adherent to their treatment with nintedanib, at 3, 6, 9 and 12 months, respectively. ***Use of LTOT over the 52-week study period*** Only 17.78% of patients were receiving LTOT at baseline and this percentage remained low throughout the study with 16.97%, 16.34%, 15.33% and 15.44% of patients receiving LTOT at 3, 6, 9 and 12 months, respectively. ***Safety analysis*** In terms of safety, 39 patients (21.67%) had at least one AE, with the most common being gastrointestinal disorders. Ten (5.56%) patients had at least one SAE. Four patients were reported to have discontinued nintedanib due to SAE and eight patients were reported to have at least one SAE that was fatal. Median survival time had not been reached up to the completion of the study observation period.
Discussion:	Based on patient demographics, the QUALIFY IPF study participants were predominantly of older age (mean ≥ 70 years) and males (~75%) similar to other IPF registries and clinical trial cohorts.

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Name of finished medicinal product: Ofev®			
Name of active ingredient: L01XE31 (Nintedanib)			
Report date: 5 Dec 2023	**Study number:** 1199-0355	**Version/Revision:** 1.0	**Version/Revision date:** N/A

Even though IPF is, by definition, a disease of unknown aetiology, a number of potential risk factors associated with its development and progression have been described, with cigarette smoking being the most commonly recognised. As such, a high prevalence of ex-smokers among IPF patients was observed in our study, which was also similar to the one reported in most IPF registries and confirms the established role of cigarette smoking as a common risk factor in IPF. Moreover, almost 1 out of 4 IPF patients reported exposure to environmental or occupational factors associated with IPF, while a family history of IPF was reported in <10% of patients.

At baseline, the SGRQ total score (mean ± SD: 32.93 ± 19.319) revealed a moderate impairment in the HRQoL of this IPF cohort relative to the population norms (total score of approximately 5.00-12.00 depending on age), with a greater impairment observed in terms of activity (mean score ± SD: 48.19 ± 22.956) compared with symptom (mean score ± SD: 32.09 ± 21.089) and psychosocial impact (mean score ± SD: 24.01 ± 20.487). Interestingly, patients in our study had somewhat less severe HRQoL impairment and a lower symptom burden than patients participating in the pivotal Phase III clinical trials of nintedanib -INPULSIS-1 and 2- (mean total SGRQ score was 39.4-39.8 points in the various arms). Such differences in both symptoms and HRQoL are likely explained by differences in baseline clinical characteristics and disease severity given that patients in our study were newly diagnosed (diagnosis up to 3 months) and thus had less advanced disease, less symptoms, better exercise capacity and eventually better HRQoL. Nevertheless, a closer look in lung function at

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baseline (FVC% predicted and DL_{CO}% predicted) revealed no apparent difference between our study patients and patients in the pivotal RCTs.

Following treatment with nintedanib for up to 12 months, no apparent improvement but rather a deterioration (decrease by up to 6 points) was observed in patients' HRQoL; changes though did not exceed the MID of 7 points. These results, are somewhat expected, taking into account that IPF is by definition a progressive disease as well as the results from the RCT trials of nintedanib that showed no improvement in HRQoL after 52 weeks of treatment with nintedanib but rather a modest effect on the delay of HRQoL decline, when compared with placebo (significant differences in favour of nintedanib in the total SGRQ score in INPULSIS-2 but not in INPULSIS-1; pooled analysis of INPULSIS-1 and -2 and TOMORROW: adjusted mean change from baseline in SGRQ total score: 2.92 with nintedanib vs 4.97 with placebo (difference: -2.05 [95% CI: -3.59, -0.50]; p = 0.0095). However, as neither group demonstrated clinically significant changes based on the MID, inferences regarding the actual impact of nintedanib on HRQoL are difficult to assess. This relatively smaller change in SGRQ may indicate a slower rate of decline in HRQoL for patients treated with nintedanib, but it did not improve HRQoL. Notably, as early as at 12 weeks of treatment, the mean ± standard error (SE) changes from baseline in the SGRQ total score were 0.38 ± 0.51 and - 0.77 ± 1.0 in patients treated with nintedanib in INPULSIS and INSTAGE (the first treatment trial in IPF with improvement in HRQoL as primary endpoint; nintedanib plus sildenafil vs monotherapy with nintedanib) trials, respectively, and 0.10 ± 0.61 in patients treated with placebo in INPULSIS, while at week 24, mean ± SE changes in SGRQ total score were 1.05 ± 0.53 and 2.42 ± 1.16 in

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patients treated with nintedanib in INPULSIS and INSTAGE trials, respectively, and 1.78 ± 0.68 in patients treated with placebo in INPULSIS.

Regarding changes from baseline in the SGRQ domains, a minor but not clinically significant improvement was observed in the symptoms domain (decrease by only 1 point), whereas deterioration was observed in the activity and psychosocial impact domains, both exceeding their corresponding MIDs at 12 months (activity: increase by 6.19 points, psychosocial impact: increase by 8.17 points). When compared with the results from the pooled analysis of the phase III RCTs, although a consistent numerical trend of reduction in deterioration from baseline with nintedanib compared with placebo was observed in the symptoms domain at 52 weeks (1.82 vs 3.67 (difference: -1.85 [95% CI: -4.22, -0.51]); p = 0.12), in the activity domain, change in our study was higher than the one observed with nintedanib and similar to the one observed with placebo (4.24 vs 6.54 (difference: -2.30 [95% CI: -4.23, -0.37]); p = 0.02) implicating no effect. As regards the psychosocial impact domain, we observed a change even higher than the one observed with placebo (3.83 vs 4.98 (difference: -1.15 [95% CI: -3.08, 0.78]); p = 0.24), a result that cannot be fully explained.

Interestingly, results from the previous stratified analyses of patients enrolled in the INPULSIS trials also suggested that although, in patients with more advanced IPF at baseline (i.e., GAP stage II/III, FVC% predicted ≤80%, DL_{CO}% predicted ≤40%, CPI > 45 or SGRQ total > 40), compared with placebo, treatment with nintedanib was associated with less deterioration in some HRQoL domains and symptoms, this effect was not apparent in patients with less advanced disease. A possible explanation is

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that SGRQ may have a greater sensitivity for change in advanced disease and not capture more subtle changes in patients with less advanced disease as in the subpopulations included in the RCTs and in our study (only newly diagnosed patients). Preliminary data from our study also implicate that, even within our newly diagnosed study population, substantial variations in changes from baseline in SGRQ may also exist, when stratified by analogous clinical characteristics at baseline (e.g., FVC% predicted, DLco% predicted and GAP stage).

Although nintedanib has not been shown to directly improve HRQoL, improving symptoms is an alternative mechanism to impact HRQoL for patients with IPF. When symptoms of dyspnoea and cough were also specifically assessed using the PROs mMRC and Cough VAS, respectively, patients treated with nintedanib show no change on the impact of dyspnoea on their daily activities, while experiencing a minor reduction in cough severity throughout the 12 months; nevertheless, no MCIDs for these PROs have been defined in IPF. The absence of apparent changes in these patient-reported symptoms severity are not surprising given that patients cough and dyspnoea were already mild at baseline and thus an effect of treatment may not be easy to detect at this less advanced stage of their disease. Similarly, no improvement but rather a numerically minor deterioration was observed in the severity of patients' anxiety symptoms as assessed by the PRO GAD-7, that is also expected given that patients had anxiety of minimal severity at baseline.

Our study also showed that adherence to treatment with nintedanib was good and remained high throughout the observation period, i.e., >70%,

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although a bit below the previously reported threshold of 90% which has been considered essential to achieve an optimal efficacy profile of nintedanib.

Finally, AE collection did not reveal any safety concerns. Although gastrointestinal disorders were the most commonly reported Aes, consistent its known safety profile, an underreporting is implicated. In particular, the frequency of diarrhoea in our study (approximately 6.8%) was lower than that observed in other real-world studies in other countries (approximately 50-60%) as well as in a previous retrospective study in Greece (45%). The underlying reason for such a discrepancy remains unclear, but we speculate that patients in our study reported diarrhoea only when it was uncontrolled or disturbing enough for them to seek medical advice and management. Moreover, it may be that higher use of, or adherence to, natural remedies or anti-diarrhoeal medications may have contributed to this difference.

In conclusion, in the QUALIFY study, newly diagnosed IPF patients being treated with nintedanib under real-life conditions showed deterioration in the overall self-reported HRQoL, in line with the progressive nature of the disease Moreover, no apparent effect on the delay of deterioration was implicated in the overall HRQoL, except from a modest effect in the symptoms burden. Nevertheless, future analyses designed based on the patients' disease clinical characteristics including severity at baseline as well as disease progression over time upon treatment with nintedanib may help to further elucidate nintedanib's potential effect on the HRQoL of patients with IPF.

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