

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: OFEV® (Nintedanib)			
Name of active ingredient: Nintedanib (ATC code: L01XE31, antineoplastic agents, protein kinase inhibitors)			
Report date: 05 February 2021	Study number: 1199-0303	Version/Revision: 1.0	Version/Revision date: NA
Title of study:	Non-Interventional study (NIS) Collecting Experiences For IPF in Taiwan		
Keywords:	Real-world setting, idiopathic pulmonary fibrosis, clinical outcomes, anti-fibrotic drugs, interstitial lung diseases		
Rationale and background:	The prevalence and incidence of IPF from 1997 to 2007 in Taiwan is 0.7–6.4 cases/100,000 and 0.6-1.4/100,000 respectively,¹ which is relatively low compared to western countries.² The median survival in Taiwan is only 0.9 year after IPF diagnosis.¹ There are two anti-fibrotic drugs conditionally recommended by the update of the IPF international consensus statement in 2015:³ nintedanib and pirfenidone. Nintedanib (OFEV®) has been on the market in Taiwan since September 2015 and pirfenidone (Pirespa®) is on market in the first half of 2016. Data on characteristics and management of IPF patients are still scarce in Taiwan. An IPF non-interventional study would help to gain a better understanding of the epidemiology of the disease and how it is currently managed.		
Research question and objectives:	The primary objective was to characterize the IPF population in Taiwan with regard to their clinical course under clinical practice conditions in Taiwan. The secondary objectives were to understand the clinical characteristics and quality of life of IPF population in Taiwan.		
Study design:	This was a non-interventional multi-center study based on newly collected data on idiopathic pulmonary fibrosis (IPF) patients in clinical practice in Taiwan. IPF patients were enrolled in a consecutive manner and data were collected in accordance with real-world clinical practice (baseline [the date of study enrolment], the first month, and approximately every 3 months afterward). Visits were in accordance with clinical needs judged by physicians. The actual enrolment period for the study was 0.5 year, and each patient was followed for 2 years.		

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Setting:	This study planned to enrol approximately 100 patients at ten sites in Taiwan. Finally, 101 patients were enrolled from 31 August 2017 to 27 February 2018. No interim analysis was conducted during the study period.		
Subjects and study size, including dropouts:	Approximately 100 patients were planned to be enrolled based on the recruitment timeframe and patient pool at 10 hospitals, the expert centers where IPF patients were mainly managed in Taiwan. Since most outcomes were continuous, this number was sufficient in order to get insights into Taiwanese IPF patients. The inclusion/exclusion criteria for this study are listed below. <u>Inclusion criteria</u> Patients were included if ALL the following criteria were met: - Newly diagnosed IPF within 6 months based upon recent ATS/ERS/JRS/ALAT IPF guideline⁴ - Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity) which needed serological test. - Assessment of IPF based on HRCT or HRCT and surgical lung biopsy, if available. - Patient ≥ 20 years of age - Written informed consent prior to participation - Patients with further follow-up possible with participating physician during planned study period - Ability to read and write in the local language <u>Exclusion criteria</u> Patients were not included if ANY of the following criteria was met: - Lung transplantation expected within next 6 months. - Inclusion in ongoing clinical trials		

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	Finally, 60.2% of patients (53/88) in the anti-fibrotic drug group completed the study, and 39.8% of patients (35/88) did not. Reasons for discontinuation included death (n = 22), adverse events (n = 5), withdrawal of consent (n = 4), lost to follow-up (n = 3), and administrative problems (n = 1). For the non-anti-fibrotic group, 46.2% of patients (6/13) completed the study and 53.8% of patients (7/13) did not. Reasons for discontinuation included withdrawal of consent (n = 3), adverse events (n = 1), lost to follow-up (n = 1), administrative problems (n = 1), and patient's decision (n = 1).		
Variables and data sources:	<u>Primary outcomes</u> Key study outcomes were to characterize lung function profile of IPF patients in clinical practice: ☐ Annual percentage of decline from baseline in FVC ☐ Annual decline from baseline in DLco ☐ Annual decline from baseline in resting and exercise SpO₂ ☐ Annual percentage of decline from baseline in TLC ☐ Annual percentage of decline from baseline in IC <u>Secondary outcomes</u> ☐ Time to first acute exacerbation of IPF after enrolment ☐ Annual change from baseline in SGRQ ☐ Annual change from baseline in CAT ☐ Annual change from baseline in 6MWT ☐ Mortality (with cause of death) and time to death <u>Statistical method</u> The analysis of primary and secondary outcomes, including results of spirometry tests, SGRQ, CAT, and 6MWT, was conducted on the basis of continuous variables, with number, mean (for annual change/decline from baseline, one mean annual change over the whole study period [0-2 years as maximum] was presented), SD, minimum, Q1 (lower quartile), median, Q2 (upper quartile), maximum value, and 95% CI included. Wilcoxon Signed Ranked test or t-test, whichever was applicable, was used to test the change from baseline under a significant level of 0.05.		

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	Time to first acute exacerbation and mortality were analyzed by Kaplan-Meier estimates, with incidence and time to event included. Time to first acute exacerbation started from the date of enrolment to the date of first acute exacerbation was recorded on the CRF. Patients with exacerbation free at the time of the last contact were censored. The time of event data was analyzed using Kaplan-Meier curves. The median, range, and 95% CI for median time were reported. Time to death was calculated from the date of enrolment to the date of death from any cause. Patients with no documented death were censored at the last time they were known to be alive or at the time of the last contact. The time of event data (overall survival, censored at 100 weeks) was analyzed by Kaplan-Meier survival method. The median, range, and 95% CI for median survival time; and survival curve were reported. Statistical analysis of all data was performed using Statistical Analysis Software (SAS®) 9.4 (SAS Institute, Cary, NC, USA). No interim analysis was conducted during the study period.		
Results:	This non-interventional, multi-center study was conducted to collect clinical data of 101 patients with IPF in Taiwan. All patients were oriental. Among them, 87.1% of patients (n = 88) received anti-fibrotic drugs, and 12.9% of patients (n = 13) did not receive the treatment. The overall IPF population aged 74.6 ± 9.14 years, had a height of 162.7 ± 7.28 cm, and had a weight of 65.3 ± 12.51 kg on average. Males accounted for the majority of patients (male: 83.2%, n = 84; female: 16.8%, n = 17). On average, the predicted FVC, predicted DL_{CO}, SpO₂, predicted TLC, and predicted IC were 73.3 ± 16.64%, 45.2 ± 20.11%, 95.8 ± 2.33%, 77.2 ± 15.50%, and 65.6 ± 17.87%, respectively. Furthermore, the mean score of SGRQ was 33.4 ± 19.77 points, and the mean CAT was 1.3 ± 7.10 points. Regarding the results of 6WMT, the mean distance, resting SpO₂, and exercise SpO₂ were 329.8 ± 96.79 meters, 94.7 ± 3.37%, and 90.9 ± 5.72%, respectively. Nearly 94% of patients were diagnosed with UIP (definite + possible) using HRCT and 11.9% had emphysema occurring in > 25% of total lung volume. In addition, these IPF patients received respiratory- (65.3%), hypertension- (20.8%), and CVD/cerebral artery occlusion-related (17.8%) medications due to comorbidities. For the patients receiving anti-fibrotic drugs (i.e., treated group, n = 88), their mean predicted FVC, predicted DL_{CO}, SpO₂, predicted TLC, and predicted IC was 69.7 ± 14.06%, 42.7 ± 19.74%, 95.5 ± 2.31%, 74.3 ± 13.25%, and 62.8 ± 15.62%, respectively. For the patients not receiving		

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		anti-fibrotic drugs (i.e., untreated group, n = 13), their mean predicted FVC, predicted DL_{CO}, SpO₂, predicted TLC, and predicted IC was 97.8 ± 10.97%, 57.5 ± 17.96%, 97.5 ± 1.69%, 100.2 ± 13.04%, and 87.5 ± 21.49%, respectively. Moreover, the mean score of SGRQ was 35.9 ± 19.74 points, and the mean CAT was 12.0 ± 7.19 points. Regarding the results of 6WMT, the mean distance, resting SpO₂, and exercise SpO₂ were 318.5 ± 90.46 meters, 94.4 ± 3.40%, and 90.7 ± 5.62%, respectively. <u>Primary outcomes</u> Regarding the annual percentage decline in lung functions, we found that following 2 years of treatments with anti-fibrotic drugs, the decline of lung function in IPF patients appeared to be lessened (FVC: -0.5 ± 10.78% at Week 52 [P = 0.505], -0.2 ± 7.74% at Week 100 [P = 0.571]; SpO₂: -0.8 ± 2.22% at Week 52 [P = 0.001], -0.2 ± 0.96% at Week 100 [P = 0.018]; TLC: -0.4 ± 9.97% at Week 52 [P = 0.073], -2.3 ± 3.76% at Week 100 [P < 0.001]; IC: -6.8 ± 10.18% at Week 52 [P < 0.001], -4.5 ± 5.00% at Week 100 [P < 0.001]). In addition, DL_{CO} was slightly increased by 0.5% in the second year (DL_{CO}: -7.3 ± 10.47% at Week 52 [P < 0.001], 0.5 ± 6.83% at Week 100 [P = 0.027]). For the untreated group (n = 13), due to the small sample size, we did not observe certain trends in lung functions (FVC: 4.1 ± 7.73% at Week 52 [P = 0.181], -2.5 ± 4.52% at Week 100 [P = 0.232]; DL_{CO}: -2.8 ± 8.27% at Week 52 [P = 0.375], -2.6 ± 6.26% at Week 100 [P = 0.938]; SpO₂: -0.8 ± 0.92% at Week 52 [P = 0.048], -0.6 ± 0.84% at Week 100 [P = 0.125]; TLC: -1.4 ± 12.18% at Week 52 [P = 0.755], -3.4 ± 6.89% at Week 100 [P = 0.281]; IC: -6.1 ± 1.73% at Week 52 [P = 0.008], -6.0 ± 2.40% at Week 100 [P = 0.031]). Therefore, results in the non-anti-fibrotic drug group should be interpreted with care due to the small sample size (n = 13). <u>Secondary outcomes</u> In terms of acute exacerbation and mortality rates in the treated group (n = 88), 21.6% of patients (n = 19) experienced acute exacerbation after a median follow-up period of 497.0 days since the study enrolment. In two years of follow-up, 31.8% of patients (n = 28) died, with a median follow-up period of 686.0 days. The leading cause of death was IPF-related symptoms (i.e., respiratory failure and acute exacerbation of IPF) occurring to 11 patients and comorbidities (i.e., pneumonia/respiratory infection, coronary heart disease, and lung cancer) occurring to seven patients. In the	

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	untreated group (n = 13), two patients experienced acute exacerbation after a median follow-up period of 521.5 days since study enrolment. In two years of follow-up, one patient died at 641 days after study enrolment. The cause of death was coronary heart disease. Concerning the results of SGRQ in the treated group (n = 88), the quality of life of patients slightly got worse in the first year (annual change: 8.4 ± 16.52 points [$P < 0.001$]) but was relatively stable in the second year (annual change: 2.6 ± 13.36 points [$P = 0.169$]). For the untreated group (n = 13), the quality of life assessed using SGRQ remained stable across 2 years of observation (Week 52: 0.2 ± 8.12 points [$P = 0.939$]; Week 100: 1.6 ± 6.17 points [$P = 0.545$]). The annual change in CAT was < 2 points in treated patients (Week 52: 1.4 ± 7.80 points [$P = 0.333$]; Week 100: 0.7 ± 4.37 points [$P = 0.245$]), indicating that the condition of airway obstruction was not exacerbated during the two years. However, the exercise capacity of treated patients seemed to get worse after 2 years (annual changes in distance in 6MWT: -7.6 ± 60.42 meters at Week 52 [$P = 0.543$], -20.7 ± 36.60 meters at Week 100 [$P = 0.046$]). In the untreated group (n = 13), the condition of airway obstruction was almost unchanged (annual changes in CAT: 0.2 ± 1.96 points at Week 52 [$P = 0.786$]; 0.7 ± 2.13 points at Week 100 [$P = 0.454$]). Stable exercise capacity of untreated patients was also observed (annual changes in distance in 6MWT: 7.1 ± 31.53 meters at Week 52 [$P = 0.733$], -2.3 ± 20.51 meters [$P = 0.898$] at Week 100). For the safety profile, 64 patients (72.7%) receiving anti-fibrotic drugs experienced AEs, and AEs were mainly graded as mild (48.4%) or severe (36.8%). Twenty-eight patients died eventually. A total of 49 SAE occurred in 29 patients. Common nintedanib-related AEs included diarrhoea (28.9%), followed by alanine aminotransferase abnormal (10.8%), aspartate aminotransferase abnormal (9.6%), decreased appetite (6.0%), and hepatic function abnormal (3.6%). Among these AEs, only one (ALT, AST abnormal) was an SAE. In the non-anti-fibrotic drug group (n = 13), four untreated patients (30.8%) experienced five AEs, and AEs were mainly graded as severe (60.0%, 3/5). Two SAEs occurred in two patients. Among the two SAEs, one SAE (cardiac arrest with unspecified cause) resulted in death.		
Discussion:	To our knowledge, this study is the first real-world research in Taiwan to investigate the clinical characteristics, outcomes, and management of IPF patients under routine practice. Generally, data on baseline FVC predicted		

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		and disease symptoms of treated patients implied that most physicians in Taiwan tends to administer anti-fibrotic drugs to IPF patients via NHI reimbursement. Regarding the treatment outcomes, we observed that the decline in lung functions (i.e., FVC) was retarded in our study, compared with previous randomized and real-world studies.⁵⁻⁹ The possible reasons for different outcomes among Taiwan and European countries may include racial differences in spite of similar baseline lung function (e.g., FVC), clinical management of IPF under routine practice, and cigarette smoking. The proportion of non-smokers was also higher in Taiwan than in European countries and Asian subgroup study.⁷⁻⁹ Smoking has been proved to be one of the key risk factors that accelerate the loss of lung function in IPF patients.¹⁰ Therefore, above factors may potentially lead to the distinct outcomes observed among our study and other studies. However, our study showed worse outcomes of acute exacerbation and quality of life (i.e., SGRQ) than those in other studies.^{5-7,11} An Asian subgroup analysis of data from the INPULSIS-ON study reported that the incidence of acute exacerbation in Asian subgroup was higher than that in the overall population, implying that Asian patients might be more likely to experience acute exacerbation than Western patients.⁹ Concerning the safety profile, no new safety issues associated with nintedanib were found in our study. Although the incidence rates of common adverse events in the current study were lower than the those recorded in the package insert nintedanib (OFEV®)¹², the mortality rate appeared to be higher in the current study than that in the Asian subgroup INPULSIS-ON study.⁶ It might be attributed to the higher incidence of acute exacerbation, compared with in the Asian subgroup study. <u>Conclusion</u> This first long-term, real-world study provides the efficacy and safety outcomes of IPF patients following the routine management in Taiwan and finds out that the decline in lung functions is lessened following the treatment of anti-fibrotic drugs. However, the incidence of acute exacerbation is still high in comparison with Western countries and other Asian studies. The ways to prevent acute exacerbation and improve the quality of life in IPF patients warrant further consideration.	

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