Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Nintedanib (Ofev) and Pirfenidone (Esbriet)			
Name of active ingredient: Nintedanib (Ofev) and Pirfenidone (Esbriet)			
Report date: 03/29/2024	**Study number:**	**Version/Revision:**	**Version/Revision date:**
Title of study:	Assessment of the Dose Reduction/Interruption and Discontinuation with Nintedanib and Pirfenidone Initiators in Patients with Idiopathic Pulmonary Fibrosis		
Keywords:	Dose reduction, discontinuation, sub-optimal therapy, antifibrotics, idiopathic pulmonary fibrosis		
Rationale and background:	Antifibrotics have demonstrated an ability to slow IPF progression, if taken according to the recommended dosing and taken continuously, in both clinical trials and real-world evidence. Previous real-world studies have compared persistence/discontinuation patterns for nintedanib and pirfenidone and found similar persistence patterns for both drugs. However, these studies have failed to consider the differential dosing regimens between these two drugs and corresponding incidence of dose reduction/interruption. This study will assess both dose reduction/interruption and discontinuation patterns for nintedanib and pirfenidone among patients with IPF.		
Research question and objectives:	Objective 1 - To assess average daily dose, and corresponding dose reduction/interruption patterns in pirfenidone initiators and nintedanib initiators separately at 6- and 12- months post-initiation in patients with IPF.		

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	Objective 2- To assess drug discontinuation patterns in pirfenidone initiators and nintedanib initiators separately at 6- and 12-months post-initiation in patients with IPF. Objective 3: To compare suboptimal dosing and discontinuation associated with patients on nintedanib versus pirfenidone in patients with IPF		
Study design:	This is a non-interventional, retrospective cohort study with existing data.		
Setting:	The study sample consisted of patients with IPF who initiated either nintedanib or pirfenidone between October 2014 up to December 2021. The study used data from the Optum Research Database (ORD), a claims database containing approximately 14 million commercial enrollees and 4 million Medicare-advantage enrollees		
Subjects and study size, including dropouts:	A total of 4,972 and 3,398 patients with a prescription of nintedanib and pirfenidone were identified in the ORD during the study identification period, respectively. After applying the final inclusion and exclusion criteria we had 1,455 and 1,389 initiators of nintedanib and pirfenidone with a diagnosis of IPF, respectively.		

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Variables and data sources:	The main outcomes for the study were incidence of sub-optimal dosing and discontinuation, calculated separately for pirfenidone and nintedanib. For each patient, average daily dose was calculated separately in each month in the post-index period. Sub-optimal dosing was defined as a dose not following the prescribing information (PI), which corresponds to a daily dose of less than 1607 mg (66.67% of full dose) for pirfenidone or less than a daily dose of 200 mg (66.67% of full dose) for nintedanib. Discontinuation of pirfenidone and nintedanib in the follow-up period was defined as a gap of at least 90 days in filling of prescription (a gap of 90 days after the prescription date + days of supply for the current prescription). We used administrative health insurance claims data from the Optum Research Database (ORD) for the period of October 1, 2013, through end of data availability (December 31, 2022). This database was chosen as it includes claims of Medicare Advantage and commercially enrolled beneficiaries.		
Results:	A total of 1,455 nintedanib and 1,389 pirfenidone users satisfied the inclusion and exclusion criteria. The mean age of the overall sample was 73.47 (SD, ±7.66). Nintedanib users had a mean age of 73.1 years (SD, ±7.8 years), were predominantly male (61.5%), were mostly Medicare beneficiaries (86.0%), residing in the South region of US (42.7%), and had a mean Charlson Comorbidity Index (CCI) score of 2.06 (SD, ±1.79). Pirfenidone users had a mean age of 73.9 years (SD, ±7.6 years), were		

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predominantly male (60.5%), were mostly Medicare beneficiaries (87.3%), residing in the South region of US (38.8%), and had a mean CCI of 2.09 (SD, ±1.79).

About 21.4% and 26.9% of nintedanib and pirfenidone users had suboptimal dosing pre-matching by month 12 after initiation, respectively. Mean time to sub-optimal dosing was 323.5 days and 300.9 days among nintedanib and pirfenidone users pre-matching, respectively. About 47.6% and 51.2% of nintedanib and pirfenidone users had drug discontinuation pre-matching by month 12 after initiation, respectively. Mean time to drug discontinuation was 257.4 days and 246.6 days among nintedanib and pirfenidone users pre-matching, respectively.

Post-matching 2,778 initiators (1389 each for nintedanib and pirfenidone) were included. Post matching, there were no significant difference between the 2 groups. Mean age was 73.4 years in the nintedanib group with 61.5% male, while mean age was 73.9 years and 60.5% male in the pirfenidone group. About 87% of patients in both groups were Medicare. The mean CCI score was 2.1 in both groups.

About 21.7% and 26.9% of nintedanib and pirfenidone users had suboptimal dosing post-matching by month 12 after initiation, respectively. Mean time to sub-optimal dosing was 323.4 days and 300.9 days among

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	nintedanib and pirfenidone users post-matching, respectively. About 47.7% and 51.2% of nintedanib and pirfenidone users had drug discontinuation post-matching by month 12 after initiation, respectively. Mean time to drug discontinuation was 257.5 days and 246.6 days among nintedanib and pirfenidone users post-matching, respectively. In the cox proportional hazards models, patients who initiated pirfenidone had 34% higher risk of sub-optimal dosing (below 66%) vs. nintedanib (Hazard ratio (HR) – 1.34 (95% CI - 1.15 to 1.56), P<0.001) Patients who initiated pirfenidone had 16% higher risk of discontinuing their drug vs. nintedanib (HR – 1.16 (95% CI – 1.04 to 1.28), P = 0.007).		

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Discussion:	Our study demonstrated that patients with IPF and treated with pirfenidone had a higher hazard of sub-optimal dosing and higher hazard of treatment discontinuation as compared to nintedanib. We believe that these differences in medication use between the two therapies could be partially attributed to the difference in dosing regimens for the two therapies. The US FDA prescribing information for nintedanib recommends nintedanib to be given as 1 capsule, twice daily. On the other hand, pirfenidone has a higher pill burden as well as higher dosing frequency compared to nintedanib. US FDA prescribing information recommends pirfenidone given three times daily. The difference in prescribing information may lead to a potentially high pill burden and greater dosing frequency for pirfenidone users which may contribute to patients regulary skipping or missing their doses as well as discontinuing therapy which may contribute to our finding of significantly higher sub-optimal dosing and treatment discontinuation for pirfenidone users compared to nintedanib. Our study is unique as it does not only look at treatment discontinuation that previously published studies have evaluated but also examines sub-optimal dosing between the two antifibrotic treatments. While treatment discontinuation is an important measure of clinical benefit, sub-optimal dosing also impacts the full benefit of antifibrotics. The US FDA prescribing information allows for a dose reduction for nintedanib, for certain groups of patients, from 150 mg per dose to 100 mg. We therefore considered any dose lower than 100mg (or 66.67% of full dose) as sub-optimal dosage. For pirfenidone however, there is no such dose reduction provision by the US FDA. Any dose lower than the full dose would be considered a sub-optimal dose. We, however, used any dose lower than 66.67% of the full dose as a sub-optimal dose for pirfenidone. We believe that this approach is conservative and still showed a statistically significant hazard for sub-optimal dosing for pirfenidone as compared to nintedanib. We think that a dose of lower than 100% for pirfenidone would have yielded even higher rates of sub-optimal dosing for pirfenidone compared to nintedanib.

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	Limitations: The study relies on administrative claims data, where laboratory data and certain clinical information are unavailable. Specifically, patients' symptoms and lab results were unavailable and therefore not studied. The severity of IPF may influence the initiation, discontinuation, and dose-reduction of an anti-fibrotic agents. Information on severity was also unavailable and not studied. In addition, this study could not ascertain reasons for discontinuations and/or dose reductions, as adverse events may not be reliably captured in the claims database, and also the reasons for drug discontinuation are not captured in the administrative claims database. Conclusion: Patient on pirfenidone had a significantly higher risk of suboptimal dosing and greater likelihood of discontinuation compared to patients on nintedanib. This study helps decision makers understand the differential complexities in dosing regimen for pirfenidone vs. nintedanib. Patients with IPF and treated with pirfenidone may not fully benefit from the therapy due to possible sub-optimal dosing and early discontinuation as compared to patients treated with nintedanib.		
Marketing Authorisation Holder(s):	NA		
Names and affiliations of principal investigators:	[redacted]		