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Non-Interventional Study (NIS) Protocol

Document Number:	**c41847952-01**
BI Study Number:	1199-0526
BI Investigational Product(s):	Nintedanib
Title:	Assessment of the Dose Reduction and Discontinuation associated with Anti-Fibrotic Medications in Patients with Idiopathic Pulmonary Fibrosis
Brief lay title:	Dose Reduction and Discontinuation with Anti-Fibrotic Medications
Protocol version identifier:	1.0
Date of last version of protocol:	Not applicable
PASS:	Pending
EU PAS register number:	Pending
Active substance:	*NA*
Medicinal product:	Nintedanib (Ofev) and Pirfenidone (Esbriet)
Product reference:	*NA*
Procedure number:	Not applicable
Marketing authorisation holder(s):	*NA*
Joint PASS:	Not applicable
Research question and objectives:	1. Primary aim - To assess average daily dose, and dose reduction/interruption patterns in nintedanib and pirfenidone initiators separately at 6- and 12- months post-initiation. 2. Secondary aim - To assess drug discontinuation patterns in nintedanib and pirfenidone initiators separately at 6- and 12-months post-initiation.

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Country(-ies) of study:	United States
Authors:	[redacted]
Marketing authorisation holder(s):	*Not applicable*
Date:	24 MAR 2023

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1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event
USD	United States Dollar

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3. RESPONSIBLE PARTIES

BI NIS [redacted]

BI NIS co-[redacted]

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4. 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)			
Protocol date: 24 MAR 2023	**Study number:** 1199-0526	**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		
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:	1. Primary aim - To assess average daily dose, and corresponding dose reduction/interruption patterns in nintedanib and pirfenidone initiators separately at 6- and 12-months post-initiation. 2. Secondary aim - To assess drug discontinuation patterns in nintedanib and pirfenidone initiators separately at 6- and 12-months post-initiation.		
Study design:	This is a non-interventional, retrospective cohort study with existing data.		

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Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Nintedanib (Ofev) and Pirfenidone (Esbriet)			
Name of active ingredient: Nintedanib (Ofev) and Pirfenidone (Esbriet)			
Protocol date: 24 MAR 2023	**Study number:** 1199-0526	**Version/Revision:**	**Version/Revision date:**
Population:	The study sample will consist of patients with IPF who initiated either nintedanib or pirfenidone between October 2014 to September 2021. The study will use data from the Optum Research Database (ORD), a claims database containing approximately 14 million commercial enrollees and 4 million Medicare-advantage enrollees		
Variables:	The main outcome of our study will be incidence of dose reduction/interruption, calculated separately for nintedanib and pirfenidone. For each patient, average daily dose will be calculated in pre-specified time-periods (for example – the first 6 months, the first 12 months, and the average daily dose calculated separately in each month since drug initiation). Incidence of dose reduction/interruption will be defined as average daily dose not following the prescribing information. As a secondary outcome, we will also assess drug discontinuation during first 6 and 12 months separately for pirfenidone and nintedanib and will be defined as a gap of at least 60 days in filling of prescription (a gap of 60 days after the prescription date + days of supply for the current prescription).		
Data sources:	We will use administrative health insurance claims data from the Optum Research Database (ORD) for the period of October 1, 2013 through end of data availability (currently September 30, 2022). This database was chosen as it includes claims of Medicare Advantage and commercially enrolled beneficiaries.		
Study size:	As this is a descriptive study, no formal calculation of sample size was performed. In a preliminary feasibility analysis using Optum data to examine sample size, we have found that 1,979 patients newly		

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Name of finished medicinal product: Nintedanib (Ofev) and Pirfenidone (Esbriet)			
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Protocol date: 24 MAR 2023	**Study number:** 1199-0526	**Version/Revision:**	**Version/Revision date:**
	initiated pirfenidone, and 2,559 patients who initiated nintedanib between 10/2014 to 12/2020. As such, this study is expected to have a sufficient sample.		
Data analysis:	Average daily dose during first 6 months and 12 months after drug initiation will be reported as means with standard deviations (SD), and median with interquartile range. Six months and 12-months daily dose categories will be presented as frequencies with percentages. Incidence of dose reduction/interruption will be reported by month of occurrence (using month 2 and onwards) and reported as frequencies with percentages. Drug discontinuation will be reported as frequencies with percentages, and time to drug discontinuation will be reported in months (mean (SD)). As this is a descriptive study, there will be no multivariable adjustment and/or direct comparison of outcomes between the pirfenidone and nintedanib cohort.		
Milestones:	The analytic database is expected to be constructed by April 20, 2023, and data analyses are expected to be completed by May 15, 2023. A draft report of the findings from this study is expected to be available for review by June 15, 2023 and completed by August 30, 2023.		

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5. AMENDMENTS AND UPDATES

None.

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6. MILESTONES

Milestone	Planned Date
First draft of summary	09/26/2022
AET summary review	10/17/2022
NPCC summary review	12/02/2022
Study protocol first draft	01/31/2023
NIS disclosure review	02/28/2023
Analytical database creation	04/20/2023
Descriptive results	05/15/2023
Final report first draft	06/15/2023

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7. RATIONALE AND BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a life-threatening rare disease characterized by decline in lung function due to progression of fibrosis in the interstitium of the lung [1]. In patients with IPF, a decline in forced vital capacity (FVC) is an important indicator of mortality [6]. The median survival of non-treated IPF patients is approximately 3 years from diagnosis [2].

Before anti-fibrotic medications became available in the US, IPF treatment mainly consisted of therapeutics that were found not to be of benefit (or even harmful), and a mainstay of care focused on symptom relief and included palliative care [3]. In October 2014, two anti-fibrotic medications, nintedanib and pirfenidone, were approved by the U.S. Food and Drug Administration (FDA) for the treatment of IPF [4, 5], which transformed the treatment of this disease. Both medications were found to reduce the rate of decline in FVC compared to placebo in phase III clinical trials [7, 8].

From the perspective of treatment, the approvals of antifibrotics for IPF were significant breakthroughs. Antifibrotics have demonstrated an ability to slow IPF progression, if taken according to the recommended dosing in the prescriber information and taken continuously, in both clinical trials [7, 8] and real-world evidence [9]. Previous real-world studies have compared persistence/ discontinuation patterns for pirfenidone and nintedanib and found similar persistence patterns for both drugs [10, 11]. However, these studies have failed to consider the differential dosing regimens between these two drugs and corresponding incidence of dose reduction and/or temporary dose interruption. Hence, this study will assess both dose reduction and/or temporary dose interruption and discontinuation patterns for pirfenidone and nintedanib among patients with IPF.

In this study, we will investigate the incidence of dose reduction/interruption beyond the label recommendations (defined as a dose not following the prescriber information (PI), which corresponds to a daily dose of 2165 mg (90% of full dose, which is 2403 mg) for pirfenidone [12, 13] or less than a daily dose of 200 mg for nintedanib (66.67% of full dose, which is 300 mg) [14]) from 10/01/2014 to 09/30/2022 using real-world data. The definition of incidence of dose reduction, which is differential for nintedanib and pirfenidone is because of –

1) In the US, the prescriber information (PI) and/or label for pirfenidone does not indicate any particular dose reduction recommended as per Food & Drug Administration (FDA). For nintedanib, reducing dose from 150 mg to 100 mg BID is part of the PI.
2) The post-hoc analysis of clinical trials showed similar slope of FVC decline for patients who reduced the dose to 100 mg BID for nintedanib, but for pirfenidone, the slope of FVC decline was steeper for patients who reduced the dose, potentially indicating that reduced dose might lead to lower benefit on FVC decline (see figures below) [12, 15]

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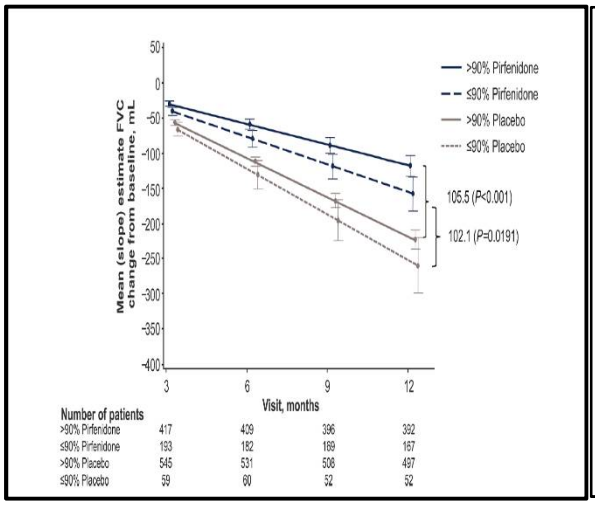

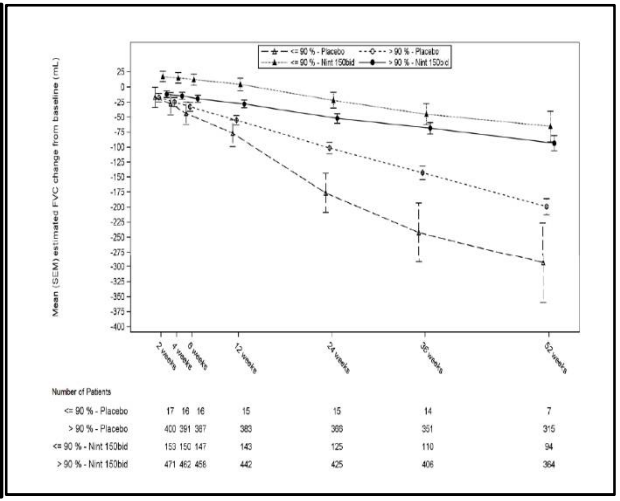

The current study may be able to demonstrate to decision makers the differential complexities in dosing regimen for pirfenidone vs. nintedanib and may reveal that IPF patients may not be receiving the full benefit of pirfenidone due to possible sub-optimal dosing, even when the patient has not discontinued the drug.

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8. RESEARCH QUESTION AND OBJECTIVES

The overarching aim of our study is to assess the incidence of dose reduction and discontinuations separately for pirfenidone and nintedanib. Specific objectives are:

Primary aim - 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.

Secondary aim - To assess drug discontinuation patterns in pirfenidone initiators and nintedanib initiators separately at 6- and 12-months post-initiation.

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9. RESEARCH METHODS

9.1 STUDY DESIGN

This study will be a retrospective cohort, descriptive study of patients with idiopathic pulmonary fibrosis (IPF). Patients with IPF who initiated either pirfenidone or nintedanib between October 2014 to September 2021 will be identified. The study will use data from the Optum Research Database (ORD), a claims database containing approximately 14 million commercial enrollees and 4 million Medicare-advantage enrollees. The date of the first prescription of either pirfenidone or nintedanib will be assigned as index date. Two separate cohorts will be created - 1) pirfenidone initiators, and 2) nintedanib initiators, and all outcomes will be assessed in the 12 months post-index period. A 12-month time-period prior to the index date will be used as the baseline period for determining the characteristics of patients in both cohorts. To allow for a 12-months baseline and follow-up periods for all patients, the span of data will be from 10/01/2013 to 09/30/2022. (Figure 1)

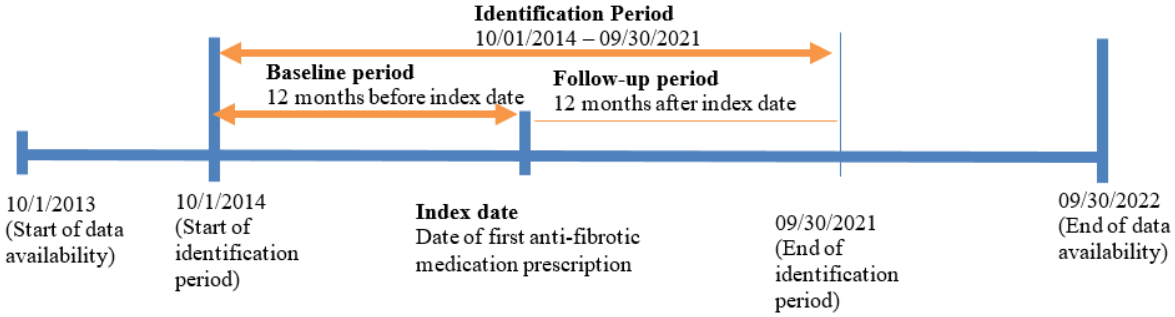

Figure 1 Study Design Schematic

The main outcome of our study will be incidence of dose reduction/interruption, calculated separately for pirfenidone and nintedanib. For each patient, average daily dose will be calculated in pre-specified time-periods (for example – the first 6 months, the first 12 months, and the average daily dose calculated separately in each month since drug initiation) (more details in section 2.6). Incidence of dose reduction/interruption will be defined as average daily dose not following the prescribing information (PI). According to the PI, the daily dose of pirfenidone is 2403 mg [13], hence the study will consider average daily dose less than 2165 mg (90% of PI dose) as dose reduction for pirfenidone [12]. For nintedanib, the daily dose allowed under prescriber information is 200 mg [14], hence less than 200 mg will be considered a dose reduction for nintedanib patients. As a secondary outcome, we will also assess drug discontinuation during first 6 and 12 months separately for pirfenidone and nintedanib and will be defined as a gap of at least 60 days in filling of prescription (a gap of 60 days after the prescription date + days of supply for the current prescription). In a sensitivity analysis, we will explore 30- and 90- days gap as a definition for drug discontinuation. As this is a descriptive study, assessment of the dose reduction and discontinuation for both drugs will be considered separately, and only descriptively, without any direct comparison between the two cohorts.

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9.2 SETTING

9.2.1 Study sites

We will use administrative health insurance claims data from the Optum Research Database (ORD) for the period of October 1, 2013 through end of data availability (currently September 30, 2021). The ORD contains enrollment information, as well as fully-adjudicated medical claims and pharmacy claims for commercial enrollees and MAPD beneficiaries. In 2018, the ORD included 14.3 million commercial enrollees with medical and pharmacy benefits and 4.3 million beneficiaries with Medicare Part C (commonly referred to as the Medicare Advantage program). Medicare Advantage beneficiaries choose to receive all of their health care services through a provider organization in lieu of Medicare Part A/B coverage (commonly referred to as Medicare Fee for Service). These plans are referred to as MAPD when combined with Medicare Part D coverage. The average enrollment duration was 31.4 and 37.3 months for commercial enrollees and MAPD enrollees, respectively. Underlying information is geographically diverse across the United States and enrollees are fairly representative of the U.S. population. Medicare beneficiaries retain a single identifier within the system and can be tracked as they change plans, or as they disenroll and reenroll over time.

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The claims history is a profile of all outpatient prescription pharmacy services provided and covered by the health plan. Pharmacy claims data include drug name, dosage form, drug strength, fill date, days of supply, financial information, and de-identified patient and prescriber codes, allowing for longitudinal tracking of medication refill patterns and changes in medications. Pharmacy claims are typically added to the research database within six weeks of dispensing.

Medical claims or encounter data are collected from all available health care sites (inpatient hospital, outpatient hospital, emergency department, physician's office, surgery center, etc.) for virtually all types of provided services, including specialty, preventive and office-based treatments. Medical claims and coding conform to insurance industry standards. Claims for ambulatory services submitted by individual providers, such as physicians, use the Health Care Financing Administration (HCFA)-1500 or Centers for Medicare and Medicaid Services (CMS)-1500 formats. Claims for facility services submitted by institutions, e.g., hospitals, use the Uniform Billing (UB)-82, UB-92, UB-04, or CMS-1450 formats. Medical claims include: multiple diagnosis codes recorded with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes; procedures recorded with ICD-9-CM and ICD-10-CM procedure codes, Current Procedural Terminology (CPT), or Health care Common Procedure Coding System (HCPCS) codes; site of service codes; provider specialty codes; revenue codes (for facilities); paid amounts; and other information. Typically, facility claims do not include medications dispensed in hospital. Approximately six months following the delivery of services is required for complete adjudication of medical data.

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9.2.2 Study population

For the primary study objective, patients included in the cohort need to meet the following criteria:

- Presence of at least one pirfenidone or nintedanib prescription during the identification period (the date of first prescription for pirfenidone/nintedanib is the index date)
- Evidence of IPF: patient with at least one inpatient or two outpatient claims (>14 days apart) with a diagnosis code for IPF (ICD-10-CM: J84.112; ICD-9-CM: 516.31) during the study period (10/01/2013 to 09/30/2022)
- At least 18 years old at the index date
- Have at least 12 months of continuous enrollment in the health plan during pre-index period, and at least 6 months of continuous enrollment in post-index period (for 12-months analysis, patients would be required to have 12 months post-index continuous enrollment)

Exclusion criteria include the following:

- Any history of lung transplant during the 12-months pre-index/baseline period
- Any claims for a skilled nursing facility, a long-term care facility or hospice care during the 12-month pre-index period
- Evidence (≥2 ICD-9-CM or ICD-10-CM diagnostic codes on different dates) of non-IPF chronic fibrosis ILD or connective tissue diseases during the 12-months pre-index period. The following conditions will be excluded: autoimmune, or connective tissue diseases (i.e., rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatopolymyositis, systemic sclerosis, Sjogren's syndrome, and mixed connective tissue disease (CTD)), sarcoidosis, and hypersensitivity pneumonitis).
- Missing demographic information (i.e., age or sex)

9.2.3 Study visits

Not applicable

9.2.4 Study discontinuation

Not applicable.

9.3 VARIABLES

9.3.1 Exposures

There is no primary exposure in this study, as this is a descriptive study evaluating dose reduction/interruption, and drug discontinuation in pirfenidone and nintedanib initiators, separately. There is no direct comparison between the two cohorts (more details in Section 9.7)

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9.3.2 Outcomes

9.3.2.1 Primary outcome

The main outcome measure of our study is the incidence of dose reduction/interruption, calculated separately for each drug. For calculating the primary outcome, we will first need to calculate the average daily dose of pirfenidone and nintedanib after drug initiation (post-index period). Specific details of calculations are –

- Average daily dose
  Average daily dose for each patient will be calculated by taking the average of total drug intake (tablet strength * number of doses) during the time between index date to the date of drug discontinuation

$$Average\ Daily\ Dose = \frac{\sum_0^n (Tablet\ Strength * number\ of\ tablets\ in\ a\ Rx\ fill)}{Time\ of\ follow-up\ \{(Date\ of\ discontinuation) - Index\ Date\}}$$

Where n = number of fills a patient has received for pirfenidone/nintedanib

- We will calculate average daily dose of pirfenidone and nintedanib separately for each month in post-index period (month 1 to 12) and will also calculate for cumulative periods of 6 months and 12 months. For all calculations, censoring events will be taken into account, with patient censored at the date of drug discontinuation, or end of 12 months.
- Six and twelve months average daily dose categories –
  For the average daily dose calculations in cumulative periods, we will be dividing the patients in following 4 categories –

  1) Dose strength less than 50%
  2) Dose strength between 51% to 66%
  3) Dose strength between 67% to 90%
  4) Dose strength above 90%

Incidence of Dose Reduction and/or temporary dose interruption

Once average daily dose is calculated for each month post-index (month 1 to 12), incidence of dose reduction/interruption will be calculated as presence of average daily dose ≤ 90% dose strength (for pirfenidone) or ≤ 66.67% dose strength (for nintedanib), as per the PI [12 – 14]. Patients will be required to have the dose reduction for at least for 60 days, to make sure that the dose reduction is not temporary.

In a sensitivity analysis, we will also evaluate temporary dose reductions, i.e., dose reduced to below the above defined dose strength only for 1 month.

In the primary analysis, patients who reduce their dose in the prior months will be allowed to discontinue the drug in future months (For example, in primary analysis, a patient can reduce their index drug dose in month 2 (i.e. dose below label recommendation for the whole month 2 and 3), and then can discontinue the drug in month 4 (or beyond). We will also evaluate the incidence of dose reduction in patients who never discontinue the index drug.

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9.3.2.2 Secondary outcomes

We will assess drug discontinuation as a secondary outcome. Pirfenidone or nintedanib discontinuation will be defined as presence of sixty or more days gap in refilling a prescription of the drug (sixty days gap counted from the date of last fill plus the days of supply for the fill). The date of last fill plus the days of supply for the fill (typically 30 days) will be designated as date of discontinuation, and time to discontinuation will be calculated as time between date of discontinuation and index date (only for patients who discontinue the drug). We will calculate the percentage of patients who discontinue each drug in first 6- and 12-months post-index period. As a sensitivity analysis, we will calculate drug discontinuation using 30 days and 90 days as allowed gap between the scripts (vs. 60 days)

We will also assess how many patients initiate either of the antifibrotic drugs (including the same drug the patient has discontinued) during the follow-up time post discontinuation of their index drug. We will separately assess initiation of the index drug vs. initiation of the other antifibrotic agent.

9.3.3 Covariates

Variable	Description
Demographic and socioeconomic characteristics	
Age	Age as of index date in whole years will be calculated based on the difference between the patient's birth date and index date.
Women	Women will be a binary indicator for whether the beneficiary was woman as indicated on the enrollment record covering the index date.
Census region	Census region will be a categorical variable defined by categorizing the beneficiary's state of residence into Census regions (Northeast, South, Midwest, West) from the enrollment record covering the index date
Index year	Index year will be a categorical variable defined as the year of the index date and will take the values 2014, 2015 2016, 2017, 2018, 2019, 2020 or 2021.
Clinical characteristics	
Charlson Comorbidity Index (CCI)	Charlson Comorbidity Index (CCI) during pre-index period: A CCI score will be calculated for each patient using diagnosis codes on medical claims during the pre-index period. The CCI was developed in 1987 based on 1-year mortality data

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Variable	Description
	from internal medicine patients, and encompasses 19 medical conditions weighted 1–6 with total scores ranging from 0–37 (Charlson ME 1987). For this study, CCI adapted for use with both ICD-9-CM and ICD-10 codes will be used (Quan H 2005). The CCI will be reported as both a continuous measure and a categorical measure (0=low, 1-2=medium, or ⩾3=high).
Pulmonary hypertension	A binary indicator for whether the beneficiary had a diagnosis code for pulmonary hypertension on at least one inpatient, or outpatient claim that occurred during the baseline period
Gastroesophageal reflux disease (GERD)	A binary indicator for whether the beneficiary had a diagnosis code for gastroesophageal reflux disease on at least one inpatient, or outpatient claim that occurred during the baseline period
Asthma	A binary indicator for whether the beneficiary had a diagnosis code for asthma on at least one inpatient, or outpatient claim that occurred during the baseline period
Sleep apnea	A binary indicator for whether the beneficiary had a diagnosis code for obstructive sleep apnea on at least one inpatient, or outpatient claim that occurred during the baseline period
Lung biopsy	A binary indicator for whether the beneficiary had a diagnosis or procedure code for a lung biopsy on at least one inpatient, or outpatient claim that occurred during the baseline period
HRCT scan	A binary indicator for whether the beneficiary had a procedure code for a high-resolution computerized tomography scan on at least one inpatient, or outpatient claim that occurred during the baseline period
Oxygen	A binary indicator for whether the beneficiary had a diagnosis, procedure revenue center code for oxygen therapy or supplemental oxygen on at least one inpatient, outpatient, skilled nursing facility, home health or durable medical

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Variable	Description
	equipment claim that occurred during the baseline period
Pulmonary rehabilitation	A binary indicator for whether the beneficiary had a procedure or revenue center code for pulmonary rehabilitation services on at least one inpatient, outpatient, skilled nursing facility, home health or durable medical equipment claim that occurred during the baseline period
Ventilator use	A binary indicator for whether the beneficiary had a diagnosis or procedure code for ventilator use on at least one inpatient, or outpatient claim that occurred during the baseline period
COPD	A binary indicator for whether the beneficiary had a diagnosis code for chronic obstructive pulmonary disease on at least one inpatient, or outpatient claim that occurred during the baseline period
Hypoxia	A binary indicator for whether the beneficiary had a diagnosis code for hypoxia on at least one inpatient, or outpatient claim that occurred during the baseline period
Pharmacy use and spending	
Medication count	The count of the number of unique outpatient prescription medications for which beneficiary has pharmacy claims during the baseline period
Total pharmacy spending	A continuous, non-negative variable representing the total amount paid by all parties for outpatient prescription medications as reported in pharmacy claims during the baseline period.
OOP pharmacy spending	A continuous, non-negative variable representing the total amount paid out-of-pocket by the beneficiary for outpatient prescription medications as reported in pharmacy claims during the baseline period.
Inpatient hospitalization use and spending	
Any inpatient stay	A binary indicator for whether a beneficiary had at least one inpatient hospitalization for any cause during the baseline period.

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Variable	Description
Inpatient stay count	A count of the number of inpatient hospitalizations for any cause a beneficiary had during the baseline period.
Inpatient length of stay	A count of the number of days (length of stay) a beneficiary was hospitalized in an inpatient facility during the baseline period. Length of stay for each inpatient hospitalization claim will be calculated as the arithmetic difference between each claim's from and through dates.
Total inpatient spending	A continuous, non-negative variable representing the total amount paid by all parties for all inpatient hospitalizations (for any cause) as reported in inpatient facility claims during the baseline period.
Outpatient facility use and spending	
Any outpatient visit	A binary indicator for whether a beneficiary had at least one claim for services provided by an outpatient facility for any cause during the baseline period.
Outpatient visit count	A count of the number of unique dates with an outpatient facility for any cause claim a beneficiary had during the baseline period.
Total outpatient spending	A continuous, non-negative variable representing the total amount paid by all parties for outpatient facility claims during the baseline period.
Medical spending	
Total Medical spending	A continuous, non-negative variable representing the total amount paid by all parties all medical claims during the baseline period, calculated as the sum of the allowed amounts on each claim.
OOP Part B spending	A continuous, non-negative variable representing the total amount paid out-of-pocket by the beneficiary for all medical claims during the baseline period.
Total spending	
Total spending	A continuous non-negative variable representing the total amount paid by all parties for all medical

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Variable	Description
	and pharmacy claims during the baseline period and will be calculated as the sum of total pharmacy and total medical spending.
Other use	
Any ED visit	A binary indicator for whether a beneficiary had at least one emergency department visit during the baseline visit.
ED visit count	A count of the number of unique dates with an emergency department visit that a beneficiary had during the baseline period.
Any pulmonology visit	A binary indicator for whether a beneficiary was treated by a specialist in pulmonary disease during the baseline period. Treatment by a pulmonologist will be identified by the presence of a pulmonary specialty code in inpatient, or outpatient claims.
Pulmonology visit count	A count of the number of unique dates with treatment by a specialist in pulmonary disease that a beneficiary had during the baseline period.

9.4 DATA SOURCES

As described above in Section 9.2.1, We will use administrative health insurance claims data from the Optum Research Database (ORD) for the period of October 1, 2013 through end of data availability (September 30, 2022). The ORD contains enrollment information, as well as fully-adjudicated medical claims and pharmacy claims for commercial enrollees and MAPD beneficiaries. In 2018, the ORD included 14.3 million commercial enrollees with medical and pharmacy benefits and 4.3 million beneficiaries with Medicare Part C (commonly referred to as the Medicare Advantage program).

9.5 STUDY SIZE

As this is a descriptive study, no formal calculation of sample size was performed. In a preliminary feasibility analysis using Optum data to examine sample size, we have found that 1,979 patients newly initiated pirfenidone, and 2,559 patients who initiated nintedanib between 10/2014 to 12/2020. As such, this study is expected to have a sufficient sample.

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9.6 DATA MANAGEMENT

Data cleaning and analysis will be executed by US HEOR group. Paper printouts of the data are not required and will not be produced. Study documents, including synopsis, protocol, final results, and publications, will be archived on the BIRDS (Boehringer Ingelheim Regulatory Documents for Submission).

9.7 DATA ANALYSIS

9.7.1 Main analysis

Baseline characteristics for the pirfenidone and nintedanib cohorts will be reported as frequencies with percentages for categorical data, and means with standard deviations (SD), and median with interquartile range will be reported for continuous variables. We will compare the baseline characteristics using Student's T-test or Wilcoxon rank-sum test for continuous variable, and chi-square test for categorical variable

Average daily dose during first 6 months and 12 months after drug initiation will be reported as means with standard deviations (SD), and median with interquartile range. Six months and 12-months daily dose categories will be presented as frequencies with percentages. Incidence of dose reduction will be reported by month of occurrence (using month 2 and onwards) and reported as frequencies with percentages. Time to drug dose reduction will be reported in months (mean (SD)). Drug discontinuation will be reported as frequencies with percentages, and time to drug discontinuation will be reported in months (mean (SD)). As this is a descriptive study, there will be no multivariable adjustment and/or direct comparison of outcomes between the pirfenidone and nintedanib cohort.

9.7.2 Post-hoc analysis

As this study is a descriptive analysis, no adjustments or direct comparison between pirfenidone and nintedanib cohort is proposed a-priori. If significant differences in the baseline characteristics between the pirfenidone and nintedanib cohorts are observed, we propose to conduct propensity score matching (PSM) to balance the baseline characteristics between the two cohort. Specifically, pirfenidone initiators will be matched to nintedanib initiators using the technique of nearest neighbor match on an estimated propensity score (caliper width of ±0.001 unit). The propensity score for this analysis will be obtained from a logistic regression model using pre-index measures to predict the probability of being in the pirfenidone initiator cohort. Pre-index measures which will be included are demographic (age, sex, census region, index year), clinical (CCI, pulmonary hypertension, COPD, asthma, GERD, HRCT scan, oxygen use, and ventilator use), and healthcare utilization measures (total pharmacy spend, total medical spend, number of pulmonology visits)

We will compare differences in baseline characteristics between the pirfenidone and nintedanib cohorts before and after propensity score matching. The success of the propensity score-matching to reduce confounding will be assessed by evaluating the standardized differences in the covariates between the study groups after matching. For each covariate, the standardized difference percent (di) will be calculated as: di = 100 * (xi − xni)/ √ ({s2i +

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s2ni}/2) where xi and xni are the sample means of the ith covariate in the pirfenidone and nintedanib cohorts, respectively, and s2i and s2ni are the corresponding sample variances. A standardized difference of <10% is considered an acceptable level of difference (or supports the assumption of balance) between the comparison groups.

We will reassess the primary and secondary outcomes in the matched cohorts (see Section 9.7.1 for more details)

9.8 QUALITY CONTROL

The following quality assurance and quality control measures will be applied to all programming that executes data extraction and transformation by US HEOR team:

- Check program logs for notes, warning messages, and errors
- Check derived data values against source data for a patient sample to ensure correct derivation
- Verify that variables needed to support tables/listings/figures/ are found in the derived data set
- Check that data fields are not truncated
- Check data points for values outside expected ranges, where appropriate
- Check that data are rounded correctly and in accordance to the analysis plan
- Check that abbreviations, range categories, and subgroups conform to the analysis plan
- Ensure the consistency of sample counts across relevant tables/listings/figures
- Check formats consistent with the analysis plan
- Ensure no typos, misspellings, or false values
- Check that summary statistics are correct; check at least one category in each summary table against the data listings
- Check that data are in accordance with the Data Plan
- Check that subgroups conform to the Data Plan
- Ensure there are no duplicate observations

9.9 LIMITATIONS OF THE RESEARCH METHODS

Several potential limitations of this study are discussed below:

- This study is based on healthcare claims data, daily dose calculations derived from monthly pharmacy fills may not represent the actual daily intake of the patient
- We could not ascertain reasons for discontinuations and/or dose reduction in this study, as adverse events may not be reliably captured in the claims database, and also the reasons for drug discontinuation are not captured in the claims database
- We will not be able to distinguish between dose reduction vs. temporary dose interruption for a patient, as the main outcome is based on calculation of daily dose based on pharmacy claims
- Due to lack of availability of laboratory data and clinical information (for example FVC% at baseline), severity of IPF, and results of the laboratory tests will not be

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observed. The severity of IPF may influence the initiation, discontinuation, and dose-reduction of an anti-fibrotic agents

- This study cannot be generalized to the entire U.S. population. ORD only covers patients with commercial insurance or Medicare Advantage plan. The findings of this study may not be applicable for patients with public insurance such as Medicare Fee-For-Service or without insurance.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

See Section 9.8

9.10.2 Study records

Not applicable.

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10. PROTECTION OF HUMAN SUBJECTS

Not applicable.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

IRB exemption has been granted to this study.

10.2 STATEMENT OF CONFIDENTIALITY

IRB exemption has been granted to this study.

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11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Given the information available within the Optum claims database for this study, extraction on adverse events data will not be conducted and only data related to the study objectives will be extracted. Therefore, information about individual adverse events will not be available. Only data on aggregate-level medication use will be analyzed.

11.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

Not applicable based on secondary use of data without any potential that any employee of BI will access individually identifiable patient data.

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12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of this study will be considered for dissemination in the form of scientific publications (e.g., an abstract/poster for presentation at a national conference, a manuscript for submission to a peer-reviewed journal).

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13. REFERENCES

13.1 PUBLISHED REFERENCES

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ANNEXES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	<Number>	11/12/2021	1276_Code_List.xlsx

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ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

1276
ENCePPChecklistforSt

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ANNEX 3. ADDITIONAL INFORMATION

Not applicable

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ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Reviewer	**NIS involving BI product(s)**	**NIS not involving BI product(s)**	
		Global NIS	**Local NIS**
NIS Lead	X	X	X
Global TM Epi	X	X	X
Global TMM / TMMA / TM Market Access	X	X	
Global Project Statistician	X	X	
Global TM RA	X		
Global PVWG Chair	X		
GPV SC	X	X	X
Global CTIS representative	X		
Local Medical Director	X (if local study)		X
Local Head MAcc / HEOR Director	X (if local study)		X
Global TA Head Epi*	X	X	
Global TA Head Clinical Development / Medical Affairs / Market Access*	X	X	
Global TA Head PV RM*	X		
RWE CoE	X	X	
PSTAT / PSTAT-MA (for NISnd only)	X	X	X
NIS DM	X	X	X
Local Head MA/Clinical Development			X (does not apply to NISed without chart abstraction)

* After review by Global TM for function

Include this Annex if signatures of external investigators are required **and/or** for studies that will not be stored in the DMS for submission documents. For non-interventional studies

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approval signatures must be obtained from the individuals as noted in section 5.1.3 “Manage NIS Protocol” in the corresponding SOP 001-MCS-90-118. If the study is a PASS, additional approvals are necessary; refer to SOP 001-MCS-90-140 “Post Authorization Safety Studies”.

Study Title:

Study Number:

Protocol Version:

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.

Note: Please insert respective signatories with regard to the SOP.

Position: [redacted] Name/Date: <[redacted] /dd mmm yyyy> Signature**:** _____

Position: NIS [redacted] Name/Date: <[redacted] / dd mmm yyyy> Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____

Position: _____ Name/Date: _____ Signature**:** _____