Non-Interventional Study (NIS) Protocol

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BI Study Number:	1199-0471
BI Investigational Product(s):	Nintedanib
Title:	Real-World Medication Adherence Trajectories to Nintedanib among Idiopathic Pulmonary Fibrosis Patients
Brief lay title:	Adherence to Nintedanib among IPF Patients
Protocol version identifier:	1.0
Date of last version of protocol:	Not applicable
PASS:	No
EU PAS register number:	Will be registered
Active substance:	Not applicable
Medicinal product:	Nintedanib (Ofev)
Product reference:	Not applicable
Procedure number:	Not applicable
Marketing authorisation holder(s):	Not applicable
Joint PASS:	No
Research question and objectives:	1) Identification of adherence patterns of nintedanib among idiopathic pulmonary fibrosis (IPF) patients. 2) Understanding characteristics of patients within each nintedanib adherence trajectory among IPF patients.
Country(-ies) of study:	United States
Author:	[redacted]

Marketing authorisation holder(s):	*NA*
Date:	12 May 2022

Page 1 of 42

1. TABLE OF CONTENTS

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
[redacted]	[redacted]
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
GBTM	Group-Based Trajectory Model
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
OOP	Out Of Pocket
PASS	Post-Authorization Safety Study
PDC	Proportions of Days Covered
SAE	Serious Adverse Event
[redacted]	[redacted]

3. RESPONSIBLE PARTIES

BI NIS [redacted]

[redacted]

4. ABSTRACT

Name of company:			
Boehringer Ingelheim			
Name of finished medicinal product: Nintedanib (Ofev)			
Name of active ingredient: Nintedanib (Ofev)			
Protocol date:	**Study number:**	**Version/Revision:**	**Version/Revision date:**
12 May 2022	1199-0471	1.0	NA
Title of study:	Real-World Medication Adherence Trajectories of Nintedanib among Idiopathic Pulmonary Fibrosis Patients		
Rationale and background:	Medication adherence is of great importance to health care stakeholders. The most common method to measure adherence in real-world settings is via the proportion of days covered (PDC) in prescription drug claims databases. However, PDC is limited by its inability to distinguish between different patterns of adherence over time. This study will use group-based trajectory modeling (GBTM) to assess adherence trajectories to nintedanib and patient characteristics associated with those trajectories. The results of this study can help providers/payers to better identify adults with IPF who are at high risk of nintedanib non-adherence. The identified non-adherence trajectories may highlight the need for a targeted intervention strategy to improve adherence in patients with each trajectory.		
Research question and objectives:	Identification of adherence trajectories of nintedanib use among IPF patients. Understanding characteristics of patients within each nintedanib adherence trajectory among IPF patients.		
Study design:	This is a non-interventional, retrospective cohort study.		

Name of company:			
Boehringer Ingelheim			
Name of finished medicinal product: Nintedanib (Ofev)			
Name of active ingredient: Nintedanib (Ofev)			
Protocol date:	**Study number:**	**Version/Revision:**	**Version/Revision date:**
12 May 2022	1199-0471	1.0	NA
Population:	The study sample will consist of community-dwelling Medicare beneficiaries with IPF who initiate treatment with nintedanib.		
Variables:	The main study outcome is nintedanib adherence trajectories. A range of predictor variables will be measured in the administrative data during the baseline and index date, including patient demographic characteristics (e.g., age, sex, race/ethnicity), Social Deprivation Index, residential location, clinical characteristics (e.g., comorbidity index, IPF-related costs and use), and all-cause health care costs and use.		
Data sources:	This study will use administrative enrollment and claims data from the U.S. federal Medicare program for beneficiaries aged 65 years and older who were continuously enrolled in Original Medicare insurance coverage, including Parts A, B and D. The study will use Medicare data covering the period from October 1, 2013 through December 31, 2019.		
Study size:	The minimum needed sample size for GBTM analysis is 500. A prior study found 1,464 Medicare beneficiaries who initiated nintedanib between 10/15/2014 and 12/31/2015 (Corral, Chang et al., 2020). By covering a longer period with the same data, this study should have sufficient sample.		
Data analysis:	In the first part, monthly trends in nintedanib PDC will be analysed via GBTM estimation, which assumes there is a fixed number of latent clusters of individuals who share a common outcome pattern. The methodology will yield estimated probabilities of cluster membership for each individual and an estimated trajectory curve over time for each cluster. In the second part, multinomial logistic models will be estimated to identify individual-level predictors of cluster membership.		
Milestones:	The analytic database is expected to be constructed by August 30, 2021, pending access to the Medicare data. Data analyses are expected to be completed by October 15, 2021. A draft report of the findings from this study is expected to be available for review by November 15, 2021 and		

Name of company:			
Boehringer Ingelheim			
Name of finished medicinal product: Nintedanib (Ofev)			
Name of active ingredient: Nintedanib (Ofev)			
Protocol date:	**Study number:**	**Version/Revision:**	**Version/Revision date:**
12 May 2022	1199-0471	1.0	NA
	completed by February 15, 2022.		

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Date
First draft of synopsis	2/1/21
VDT synopsis review	2/25/21
IET synopsis review	4/23/21
Kick-off meeting with vendor	05/07/21
NPCC synopsis review	05/21/21
Study protocol first draft	06/01/21
Study protocol VDT and NIS review	07/22/21
Study protocol NPCC review	08/17/21
Study protocol final draft	08/20/21
Analytical database creation	08/30/21
Descriptive results to BI	09/15/21
GBTM results to BI	10/15/21
Final report first draft	11/15/21
Final report comments from BI	01/15/22
Final report final draft	02/15/22

7. RATIONALE AND BACKGROUND

Medication adherence is of great importance to health care stakeholders based on increasing evidence of prevalence of non-adherence to chronic medications in the United States (Desai et al., 2019) and increasing evidence that adherence is associated with better health outcomes and lower costs (Cutler et al., 2018). There are several ways by which adherence to medications can be measured. Each of these methods has its own strengths and limitations (Forbes et al., 2018). Direct methods, which include blood drug assays, and direct observation of the patients are expensive, laborious, and time intensive (Farmer, 1999). In real-world settings, use of prescription claims databases, patient self-report, pill counts, and electronic monitoring are the common measures of adherence (Lam and Fresco, 2015). The most common method to measure adherence in real-world settings is via the proportion of days covered (PDC) in prescription drug claims databases (Harbaugh and Cooper, 2018). PDC has been defined as the number of days supplied of a specific medication in the follow-up period divided by the total number of days during follow-up, multiplied by 100 to yield a percentage from 0%–100% (Raebel et al., 2013).

Although PDC is useful in that it offers in a single number a metric of medication adherence over a predefined period of time, it is also limited because it does not distinguish between different patterns of adherence over that same period (Alhazami et al., 2020). For example, a patient who took medications every other day for a year would have a PDC of 50%; likewise, a patient who took the medication for the first 6 months uninterrupted and then not again for the remainder of the year would also have a PDC of 50%. Distinguishing these different patterns is critical to understanding adherence to prescription medication and designing interventions to improve adherence.

One alternative is to detect trajectories of adherence over time across patients using group-based trajectory modeling (GBTM) (Nagin and Odgers, 2010). GBTM has been applied with increasing frequency for this purpose in several conditions (Alhazami et al., 2020; Bateman et al., 2016; Dillon et al., 2018; Feldman et al., 2018; Franklin et al., 2018; Franklin et al., 2015; Franklin et al.; 2013; Hargrove et al., 2017; Juarez et al., 2015; Kim et al., 2017; Li et al., 2014; Lo-Ciganic et al., 2016; MacEwen et al., 2016; Paranjpe et al., 2020; Vadhariya et al., 2019; Wang et al., 2019; Zongo et al., 2019). In most of these studies, monthly PDC was assessed for each patient , and a GBTM was fit on the patient-level sequences of monthly PDC values to identify a best-fitting set of adherence trajectories as well as, for each patient, estimates of the probability of belonging to each trajectory group.

Studies that examine adherence trajectories with GBTMs frequently include analyses of the predictors of patients' membership in trajectory groups. Individual characteristics that have been observed to be related to adherence trajectories include age, race, sex, disease severity, comorbidity burden, educational attainment, and socioeconomic status (Alhazami et al., 2020).

Adherence to nintedanib has been evaluated in a few recent studies in the United States. Recent observational studies of nintedanib and pirfenidone suggest that despite different side-

effect profiles, adherence to and persistence with therapy are similar. Adherence (measured as PDC ≥ 80%) of nintedanib during one year has been estimated at 60.5% (Corral, Chang, et al., 2020), 51% (Corral, DeYoung, and Kong, 2020), and 71.3% (Ipatova et al., 2019). No studies to our knowledge have analyzed nintedanib adherence using GBTM or comparable methods nor have any studies assessed predictors of adherence.

Therefore, the objective of this study is to assess nintedanib adherence trajectories using GBTMs and understand characteristics of patients within each trajectory. The results of this study can help providers and payers to better identify adults with IPF who are at high risk of nintedanib non-adherence. The identified non-adherence trajectories may highlight the need for a fit-for-targeted intervention strategy to improve adherence in patients within each trajectory.

8. RESEARCH QUESTION AND OBJECTIVES

This study has two objectives:

1. Identification of adherence trajectories of nintedanib among IPF patients.
2. Understanding characteristics of patients within each nintedanib adherence trajectory among IPF patients.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is a non-interventional cohort study using existing administrative data from the U.S. Medicare program. There will be no comparison groups nor any exposure variables. As shown in Figure 1, the study sample will consist of community-dwelling Medicare beneficiaries with IPF who initiated treatment with nintedanib between 10/01/2014 to 12/31/2018. To allow for a one-year baseline period and one-year follow-up period for all beneficiaries who initiated nintedanib between 10/01/2014 and 12/31/2018, the span of data will be from 10/01/2013 to 12/31/2019.

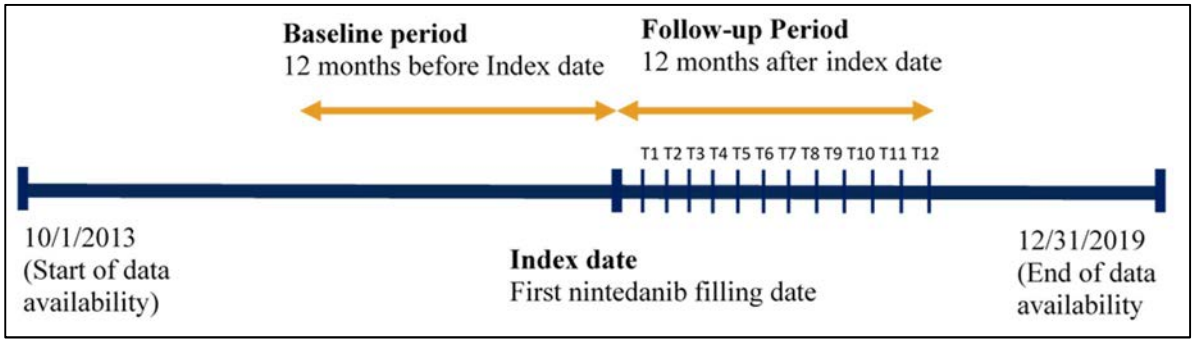

Figure 1 Study design schematic

9.2 SETTING

9.2.1 Study sites

The study will use 100% Medicare claims and enrollment data from the U.S. Medicare program on community-dwelling beneficiaries continuously enrolled in traditional, or fee-for-service, Medicare insurance coverage for inpatient hospital, skilled nursing and outpatient facility services (Part A), physician and other professional services (Part B), and outpatient prescription drugs (Part D).

The enrollment file contains monthly information on individuals' enrollment in each part of Medicare, demographic information, residential location (at the 5-digit ZIP Code level), and date of death.

Claims data are available for all medical services covered by the program and are organized into data files based on the nature and source of the claim. The Inpatient, Outpatient, and SNF files include institutional claims from hospitals for inpatient and outpatient services and from nursing homes for short-stay "skilled" admissions, respectively. The Carrier file includes fee-for-service claims submitted by professional providers, including physicians, physician assistants, clinical social workers, nurse practitioners. (Claims for some organizational providers, such as free-standing facilities are also found in the Carrier file. Examples include independent clinical laboratories, ambulance providers, free-standing ambulatory surgical centers, and free-standing radiology centers.) Separate files include claims for durable medical equipment, home health visits and hospice care.

Pharmacy Part D claims include complete prescription drug information, and all standardized prescription-level fields collected on a typical pharmacy claim (e.g., date of fill or refill, drug name and class, strength, quantity, and days' supply).

9.2.2 Study population

Inclusion criteria:

- Newly initiated nintedanib during 10/01/2014 to 12/31/2018 (see tab "T1 ANTIFIB RX" in standalone document "Code_List.xlsx")
- Were at least 66 years old as of the date of their first nintedanib prescription claim (index date)
- Qualified for Medicare based on age
- Had at least 12 months of continuous enrollment in Medicare Parts A, B and D before (baseline period) and 12 months after the index date (follow-up period)
- Had at least one inpatient or two outpatient claims ($\geq$14 days apart) with a diagnosis code for IPF (ICD-10-CM: J84.112; ICD-9-CM: 516.31) during the baseline period (see tab "T3 IPF DX" in standalone document "Code_List.xlsx

Exclusion criteria:

- Had any history of pirfenidone or nintedanib use during the baseline period (see tab "T1 ANTIFIB RX" in standalone document "Code_List.xlsx")
- Had any history of lung transplant during the baseline, index date or follow-up periods (see tabs "T4 LUNG_TRANS PR" and "T5 LUNG_TRANS DX" in standalone document "Code_List.xlsx")
- Had any claims for skilled nursing facility, long-term care facility or hospice during the baseline, index date or follow-up period
- Had evidence (≥2 ICD-9-CM or ICD-10-CM diagnosis codes on different dates) during the baseline period of any of the following conditions: lung cancer, autoimmune, or connective tissue diseases (i.e. rheumatoid arthritis (RA), sarcoidosis, systemic lupus erythematosus (SLE), dermatopolymyositis, systemic sclerosis, Sjogren's, and mixed connective tissue disease (CTD)) during the baseline period (Appendix-1)
- Had dual eligibility of Medicare and Medicaid.
- Had history of using pirfenidone at the same time with nintedanib during follow-up

9.2.3 Study visits

Not applicable.

9.2.4 Study discontinuation

Not applicable

9.3 VARIABLES

9.3.1 Exposures

This is a study of nintedanib adherence patterns, and all the included patients will be patients with a prescription claim for nintedanib.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The main outcome of this study is adherence trajectories to nintedanib. This study will use the GBTM method to identify trajectories of adherence.

For this purpose, first claim for nintedanib will be identified in the Part D claims file based on the presence of an 11-digit NDC code for nintedanib (00597-0143-60, 00597-0145-60 [CanMED, 2021]). Nintedanib supply calendars will be constructed for the all twelve 30-day time intervals following the individual's nintedanib initiation date based on each claim's service date and days' supply.

-Supply will be assigned as 1 for each day with positive days' supply of nintedanib.

-If a patient has multiple prescription claims for nintedanib on the same date, the maximum of days' supply will be calculated across the claims and applied to the supply calendar.
-Stockpiling will be implemented if a patient has prescription claims for nintedanib that overlap. Days' supply for the newer claim will be postponed to the first day after end of the older claim's supply.
-For each 30-day month following the nintedanib initiation date, PDC will be calculated as the sum of days with supply divided by 30.

In this way, we are able to calculate monthly nintedanib proportion of days covered. By using the twelve 30-days PDC values as outcomes in the GBTM, the probabilities that a given individual is in each of the latent clusters will be calculated by the GBTM estimation procedure. GBTMs will be estimated using the Stata plugin `traj` (Jones and Nagin, 2013).

9.3.3 Covariates

The index date will be defined as the date of the beneficiary's first Part D claim for nintedanib. The baseline period will consist of the 360 consecutive days ending the day before the index date. The follow-up period will consist of the 360 consecutive days starting with the index date.

Variable	Description
Demographic and socioeconomic characteristics	
Age	Age as of index date in years rounded to the nearest whole number will be calculated based on the difference between the beneficiary's birth date and index date.
Age group	Age group will be a categorical variable for age defined as one of 65–74, 75–84, 85+.
Female	Female will be a binary indicator for whether the beneficiary was female as indicated on the enrollment record covering the index date.
Race	Race will be a categorical variable for the beneficiary's self-reported race/ethnicity taking the categories Non-Hispanic White, Black or African-American, Other, Asian/Pacific Islander, Hispanic, American Indian/Alaska Native, and unknown race from 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 (see tab "T2 STATES" in

Variable	Description
	standalone document "Code_List.xlsx").
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 or 2018.
Social deprivation index	Social deprivation index will be a continuous variable ranging between 0 and 100 representing the Social Deprivation Index for the beneficiary's residential ZIP Code as calculated by the [redacted]. Social Deprivation Index "is a composite measure of seven demographic characteristics collected in the American Community Survey (ACS): percent living in poverty, percent with less than 12 years of education, percent single parent household, percent living in rented housing unit, percent living in overcrowded housing unit, percent of households without a car, and percent non-employed adults under 65 years of age." This version was calculated in 2015 using data from 2015 and updates the original version created by Butler et al. (2013). Higher values for the Social Deprivation Index indicate more social deprivation.
Clinical characteristics	
Combined comorbidity index	The combined comorbidity index will be a continuous comorbidity score ranging from 0 to 26 as measured from comorbidity diagnosis codes in any position on inpatient, outpatient and Carrier claims that occurred during the baseline period. The combined comorbidity score is based on research by Gagne et al. (2011) and Sun et al. (2017) to identify the conditions in the union of the two most-popular comorbidity indexes used in administrative claims data, the Charlson index and the Elixhauser index. For a sample of Medicare beneficiaries, Gagne et al. (2011) found that a subset of 20 conditions predicted mortality at 30, 60, 90 and 180 days, and 1 year more accurately than either of the two indexes on their own. Moreover, unlike the Charlson and Elixhauser indexes, Gagne et al.'s (2011) combined index is not conditioned on inpatient hospital admission.

Variable	Description
	The 20 conditions in Gagne et al.'s (2011) combined comorbidity index (with their weights in parentheses) include: - Metastatic cancer (5), - Congestive heart failure (2), - Dementia (2), - Renal failure (2), - Weight loss (2), - Hemiplegia (1), - Alcohol abuse (1), - Any tumor (1), - Cardiac arrhythmias (1), - Chronic pulmonary disease (1), - Coagulopathy (1), - Complicated diabetes (1), - Deficiency anemia (1), - Fluid and electrolyte disorders (1), - Liver disease (1), - Peripheral vascular disease (1), - Psychosis (1), - Pulmonary circulation disorders (1), - HIV/AIDS (−1), and - Hypertension (−1).
Pulmonary hypertension	A binary indicator for whether the beneficiary had a diagnosis code for pulmonary hypertension on at least one inpatient, outpatient or Carrier claim that occurred during the baseline period (see tab "T7 PULM_HTN DX" in standalone document "Code_List.xlsx").
Gastroesophageal reflux	A binary indicator for whether the beneficiary had a diagnosis code for gastroesophageal reflux disease on at least one inpatient, outpatient or Carrier claim that occurred during the baseline period (see tab "T8 GASTR_REFLX DX" in standalone document "Code_List.xlsx").
Asthma	A binary indicator for whether the beneficiary had

Variable	Description
	a diagnosis code for asthma on at least one inpatient, outpatient or Carrier claim that occurred during the baseline period (see tab "T9 ASTHMA DX" in standalone document "Code_List.xlsx").
Sleep apnea	A binary indicator for whether the beneficiary had a diagnosis code for obstructive sleep apnea on at least one inpatient, outpatient or Carrier claim that occurred during the baseline period (see tab "T10 SLEEP_APNEA DX" in standalone document "Code_List.xlsx").
Lung biopsy	A binary indicator for whether the beneficiary had a diagnosis or procedure code for a lung biopsy on at least one inpatient, outpatient or Carrier claim that occurred during the baseline period (see tab "T11 LUNG_BIOPSY PR" in standalone document "Code_List.xlsx").
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, outpatient or Carrier claim that occurred during the baseline period (see tab "T12 HRCT_SCAN PR" in standalone document "Code_List.xlsx").
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, Carrier, skilled nursing facility, home health or durable medical equipment claim that occurred during the baseline period (see tabs "T13 OXYGEN PR", "T14 OXYGEN REV" and "T15 OXYGEN DX" in standalone document "Code_List.xlsx").
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, Carrier, skilled nursing facility, home health or durable medical equipment claim that occurred during the baseline period (see tabs "T16 PULM_REHAB PR" and "T17 PULM_REHAB REV" in standalone document "Code_List.xlsx").
Ventilator use	A binary indicator for whether the beneficiary had a

Variable	Description
	diagnosis or procedure code for ventilator use on at least one inpatient, outpatient or Carrier claim that occurred during the baseline period (see tabs "T18 VENT_USE PR" and "T19 VENT_USE DX" in standalone document "Code_List.xlsx").
COPD	A binary indicator for whether the beneficiary had a diagnosis code for chronic obstructive pulmonary disease on at least one inpatient, outpatient or Carrier claim that occurred during the baseline period (see tab "T20 COPD DX" in standalone document "Code_List.xlsx").
Hypoxia	A binary indicator for whether the beneficiary had a diagnosis code for hypoxia on at least one inpatient, outpatient or Carrier claim that occurred during the baseline period (see tab "T21 HYPOXIA DX" in standalone document "Code_List.xlsx").
Pharmacy use and spending	
Medication count	The count of the number of unique outpatient prescription medications for which beneficiary has Part D 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 Part D 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 Part D 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.
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

Variable	Description
	hospitalizations (for any cause) as reported in inpatient facility claims during the baseline period. This is calculated as the sum of the Medicare payment amount, the Medicare per diem amount, the non-Medicare payer amount, and the patient OOP amount.
OOP inpatient spending	A continuous, non-negative variable representing the total amount paid out-of-pocket by the beneficiary 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. This is calculated as the sum of the Medicare payment amount, the blood deductible liability amount, the non-Medicare payer amount, and the patient OOP amount.
OOP outpatient spending	A continuous, non-negative variable representing the total amount paid out-of-pocket by the beneficiary for services as reported in outpatient facility claims during the baseline period.
Home health use and spending	
Any home health	A binary indicator for whether a beneficiary had at least one claim for home health services during the baseline period.
Home health count	A count of the number of home health visits a beneficiary had during the baseline period, calculated by summing the total visit count on each claim across claims.
Total home health spending	A continuous, non-negative variable representing the total amount paid by all parties for home health claims during the baseline period. This is calculated as the sum of the Medicare payment amount, the blood deductible liability amount, the non-Medicare payer amount, and the patient OOP amount.

Variable	Description
Part B spending	
Total Part B spending	A continuous, non-negative variable representing the total amount paid by all parties for Carrier and Durable Medical Equipment 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 Carrier and Durable Medical Equipment claims during the baseline period.
Total spending	
Total medical spending	A continuous non-negative variable representing the total amount paid by all parties for all medical services during the baseline period, including inpatient, outpatient, home health and Part B.
Total spending	A continuous non-negative variable representing the total amount paid by all parties for all medical 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. Note that hospitals bill for emergency department visits on either the Inpatient or Outpatient facility claims, as described by [redacted] here. Thus, emergency department visits will be identified in inpatient and outpatient facility claims via the presence of revenue center codes [redacted] and [redacted].
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, outpatient and Carrier 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.

Variable	Description
Pulmonology prescriber	A binary indicator for whether the clinician who prescribed the beneficiary's index nintedanib medication was a pulmonologist, as documented in the Part D Prescriber Characteristics file for the index nintedanib claim.

Inflation Adjustment

All dollar-denominated variables will be inflated to 2019 USD using the Consumer Price Index, which is listed in Table 1.

Table 1 Consumer price index for medical care implicit price deflator

Year	Inflation Multiplier
2013	1.180
2014	1.152
2015	1.123
2016	1.077
2017	1.057
2018	1.038
2019	1.000

Source: U.S. BUREAU OF LABOR STATISTICS; Bureau of Labor Statistics Data (bls.gov), July 22, 2021.

9.4 DATA SOURCES

As described above in Section 9.2.1, all variables will be constructed from the 100% Medicare claims and enrolment data from the U.S. Medicare program for the individuals meeting the sample selection criteria. To allow for a one-year baseline period and one-year follow-up period for all beneficiaries who initiated nintedanib between 10/01/2014 and 12/31/2018, the Medicare will span 10/01/2013 through 12/31/2019.

9.5 STUDY SIZE

This study will use the GBTM technique to adherence pattern. Based on empirical results generated by resampling of population data, the maximum likelihood estimates obtained in group-based trajectory models provide reasonably close estimates of their true population values and have approximately normal distributions, even when estimated with a sample size as small as n = 500 (Loughran and Nagin, 2006). A prior study found 1,464 Medicare

beneficiaries who initiated nintedanib between 10/15/2014 and 12/31/2015 (Corral, Chang et al., 2020). By covering a longer period with the same data, this study should have a sufficient sample.

9.6 DATA MANAGEMENT

Pursuant to requirements guiding participation in the [redacted] Innovator program, [redacted] staff will access the Medicare claims and enrolment data only through the [redacted]. As such, [redacted] will not directly possess any beneficiary-level [redacted] data, and the only data to be downloaded from the [redacted] will be summary-level statistics.

[redacted] staff will access the [redacted] environment via the VMware Horizon Client (or whichever client is mandated by [redacted]) from dedicated [redacted] computers. All [redacted] computers are secured with Microsoft BitLocker (for hard drive encryption at rest), Microsoft Azure Active Directory (to implement local security policies, including password management), BitDefender (anti-virus software), and LoJack (for computer tracking and remote wiping if ever needed).

All data manipulation and analysis will be conducted on the [redacted] environment remotely by [redacted] staff. Data manipulation and analysis will be conducted using SAS software ([redacted]) and Stata software ([redacted]).

9.7 DATA ANALYSIS

9.7.1 Main analysis

The objective of the main analysis is to identify the adherence patterns of nintedanib among IPF patients. The unit of analysis will be the individual beneficiary, each of whom will have twelve 30-days time intervals measurments of nintedanib PDC spanning the follow-up period. The 12 PDC values (PDC01–PDC12) will be characterized descriptively with measured of central tendency (mean, median), spread (min, max, interquartile range), and proportions of beneficiaries with PDC in each of 0 to <20%, 20 to <40%, 40 to <60%, 60 to <80%, and 80 to 100%.

GBTM will be used to explore the presence of distinct trajectories based on the change in medication adherence over time. The output of GBTM will include estimated probabilities of cluster membership for each individual and an estimated trajectory curve over time for each cluster. Different models will be used to identify 2 to 5 groups by using either cubic, quadratic, or quartic terms. The final models will be based on Bayesian information criteria, and Nagin's criteria for model adequacy (Nagin and Odgers, 2010), with consideration given to group size such that the proportion of patients in each group is not less than 5% of the total sample. The output of the final model will give us the estimated average trajectory for each group, as well as the estimated probabilities of membership in each trajectory for each patient. We will decide the number and shapes of trajectories based on both model fit,

ensuring enough class size and clinical usefulness (Hickson, et al, 2020). An example of using GBTM for assessing medication adherence is provided in Figure2 .

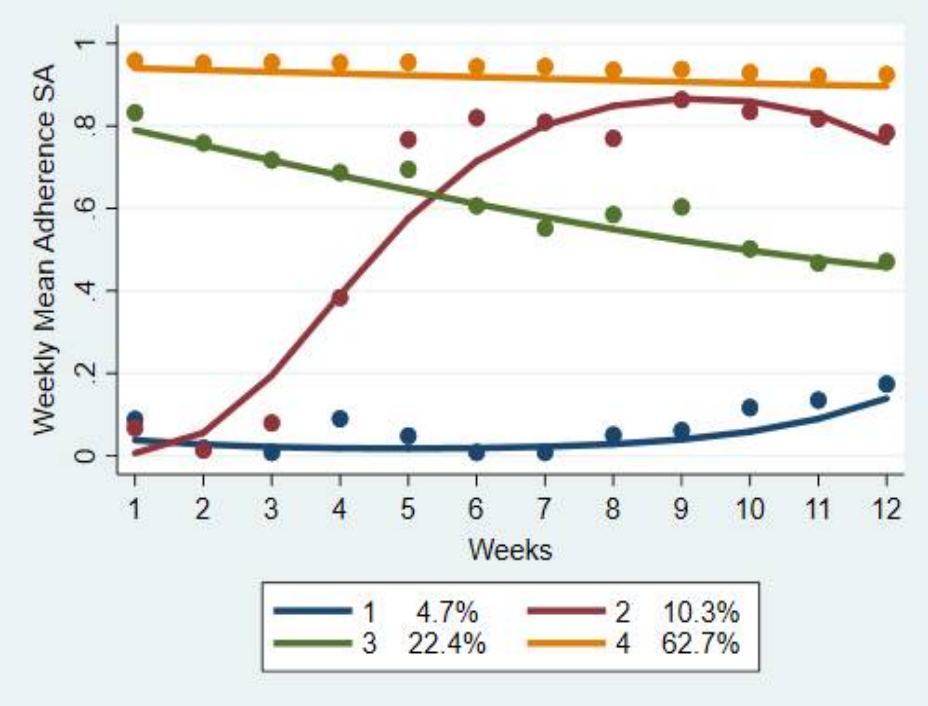

Figure 2 GBTM medication adherence example

Two sensitivity analyses will be conducted:

- First, the analysis will be repeated for beneficiaries who have positive PDC in the fourth month. In these models, only data from months 4 through 12 will be used to estimate the GBTMs because PDC01–PDC03 will have been used to condition the estimation sample.

- Second, the GBTMs will be re-estimated using as the outcome continuous PDC (for the same twelve30-day time intervals) and the beta distribution (Elmer, Jones and Nagin, 2018).

For each trajectory group identified, the mean PDC and the percent of beneficiaries in that group who discontinued nintedanib will be calculated.

9.7.2 Additional analysis

The objective of the additional analysis is to understand characteristics of patients within each nintedanib adherence trajectory among IPF patients. The unit of analysis will be the individual beneficiary, and the outcomes will be the vector of estimated probabilities of

cluster membership from a given GBTM. The predictor variables will be the baseline covariates (Section 9.3.3).

The distributions of the covariates will be characterized with descriptive statistics, including frequencies and percentages for discrete or categorical variables, and means, standard deviations, medians, and interquartile ranges for continuous variables.

Associations between the predictors and the probabilities of trajectory membership will be quantified using fractional multinomial logit models estimated via quasi-maximum likelihood (Papke and Wooldridge, 1996). Associations will be calculated both as odds ratios (exponentating the fractional multinomial logit model's coefficients) and average marginal effects on the probability scale.

9.8 QUALITY CONTROL

The Medicare administrative data collection occurred in the past and the data will be obtained from [redacted]. No additional insight into the data collection procedures is available beyond that which has been published by [redacted]. As a result, we are relying on quality control measures implemented by [redacted] during data collection.

[redacted] has established protocols for quality control of analyses. All analyses are audited before the finalization of results. The auditor will independently review the conceptual and technical elements of the analysis with a critical eye to identifying any flaws or potential errors.

The auditor will understand the goal of the analysis and the expected results, and then review each step of the [redacted] data analysis audit checklist (available upon request). The auditor will keep a list of questions or issues and then meet with the project lead to discuss any findings. If errors or issues are found that change the results, the auditor will perform an incremental audit to ensure that changes have been implemented properly and any change in results aligns with expectations about magnitude and direction.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This study has several limitations, which include:

- Absence of data on some behavioral factors (e.g. patient-physician communication, fear of disease/side effects, and family support) which may affect non-adherence.
- Reliance on prescription fill data to define adherence may not capture the actual use of the medication.
- In this study, patients who had 12 months of continued fee-for-service enrollment of Parts A, B, and D before and after index dates were included.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

The following quality assurance and quality control measures will be applied to all programming that executes data extraction and transformation by [redacted]:

- 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

9.10.2 Study records

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

Not applicable based on secondary use of data without access to identifiable patient data.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

Not applicable to this study.

10.2 STATEMENT OF CONFIDENTIALITY

Not applicable to this study

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Given the information available within the Medicare 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 analysed.

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 or [redacted] will access individually identifiable patient data.

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).

13. REFERENCES

13.1 PUBLISHED REFERENCES

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14. ANNEXURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	<Number>	July 7 2021	Code_List.xlsx

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

A copy of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for Study protocols available at website: encepp.eu/standards_and_guidances/index.html completed and signed by the main author of the study protocol should be included in Annex 2.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist, Revision 1:

“Study start” means “Start of data collection”
“Study progress” means “Progress report(s)”
“Study completion” means “End of data collection”
“Reporting” means “Final report of the study results”

ANNEX 3. ADDITIONAL INFORMATION

Additional annexes may be included if necessary.

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 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: __PI_ Name/Date: < > Signature**:** _____

Position: NIS Lead Name/Date: < > Signature**:** _____

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

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

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

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

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