Boehringer Ingelheim

Non-Interventional Study (NIS) Protocol

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Product reference:	*<Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study, if applicable>*
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Marketing authorisation holder(s):	*<Marketing authorisation holder(s) which initiate(s), manage(s) or finance(s) the study>*
Joint PASS:	No

Research question and objectives:	1) To quantify the association between nintedanib adherence trajectory group (as measured from a group-based trajectory model or GBTM) and health care resource use, with a focus on inpatient hospitalization, among patients with IPF. 2) To quantify the association between a patient's nintedanib adherence trajectory group (as measured from a GBTM) and their medical costs among patients with IPF.
Country(-ies) of study:	United States
Author:	[redacted]
Marketing authorisation holder(s):	*<Name, address and contact details of the marketing authorisation holder(s)>*
Date:	05/09/2023

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2. LIST OF ABBREVIATIONS

CI	Confidence Interval
[redacted]	
ENCePP	European Network of Centres for Pharmacoepidemiology and
PVG	Pharmacovigilance
GBTM	Group-based Trajectory Modelling
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
PDC	Proportion of Days Covered
[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: 9 May 2023	**Study number:** 1199-0520	**Version/Revision:** 5.0	**Version/Revision date:** 19 April 2023
Title of study:	Economic burden associated with nintedanib non-adherence among Medicare beneficiaries with IPF		
Rationale and background:	Recent systematic reviews found links between medication non-adherence and higher healthcare spending (Cutler et al., 2018) and elevated risks of inpatient hospitalization and mortality (Walsh et al., 2019). To our knowledge, however, there have been no studies examining the association between non-adherence and economic burden specific to nintedanib, antifibrotics, or idiopathic pulmonary fibrosis (IPF). A prior study by this team quantified nintedanib adherence trajectories using group-based trajectory modelling (GBTM) and identified characteristics of patients associated with membership in each trajectory group. A handful of existing studies examine associations between medication non-adherence as measured from GBTM and coincident or subsequent health care resource use, although none were specific to the setting of interest here. This study seeks to build on our prior study and fill that gap in knowledge. We expect the findings from this study to be highly relevant to clinicians and payers to help optimize care in a cost-effective manner.		
Research question and objectives:	1) Assess the association between nintedanib adherence trajectory group (as measured from a GBTM) and health care resource use, with a focus on inpatient hospitalization, among patients with IPF. 2) Assess the association between a patient's nintedanib adherence trajectory group (as measured from a GBTM) and their medical costs among patients with IPF.		
Study design:	This is a non-interventional, retrospective cohort study.		

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Protocol date: 9 May 2023	**Study number:** 1199-0520	**Version/Revision:** 5.0	**Version/Revision date:** 19 April 2023
Population:	The study sample will consist of community-dwelling Medicare beneficiaries with IPF who initiate treatment with nintedanib.		
Variables:	The main exposure will be a five-category measure of adherence trajectory to nintedanib in the year following initiation. Outcomes will reflect inpatient hospitalization (any and number of days) and health care spending for both all-cause and IPF-related care. A range of covariates will be measured during the baseline period and at the index date, including baseline patient demographic characteristics (e.g., age, sex, race/ethnicity), residential location, clinical characteristics (e.g., comorbidity index, IPF-related health care 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, 2020.		
Study size:	Based on our prior study, the sample for analysis of the primary outcomes will consist of 1,798 Medicare beneficiaries with IPF who initiated nintedanib between October 1, 2014, and December 31, 2018. The sample available for the secondary outcomes will be smaller by an unknown amount due to loss to follow-up.		
Data analysis:	Mean health care cost and use outcomes will be compared between pairs of nintedanib adherence trajectory membership categories using a regression modeling framework. Unadjusted means will be compared first using an "empty" linear regression model specification (with no covariates or weights). Adjusted means will then be compared using a "doubly robust" generalized linear model (GLM) specification. Potential confounding by observed covariates will be addressed in two ways to achieve double robustness. The first way will be to calculate observation-level inverse propensity weights that balance covariates		

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	across exposure categories. The second way will be through regression adjustment; that is, observed covariates will be added to the GLM specification.		
Milestones:	Final report of this study is expected to be available for review by May 15th, 2023.		

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Final report	05/15/2023
Poster draft	TBD
Poster BI approval (all steps in DataVision)	TBD
Manuscript draft	TBD
Manuscript BU approval (all steps in DataVision)	TBD
Publication	TBD

7. RATIONALE AND BACKGROUND

It is taken as self-evident in the medical community that medication non-adherence leads to negative outcomes; as C. Everett Koop said, "Drugs don't work in patients who don't take them" (Osterberg and Blaschke, 2005). Recent systematic reviews of the published literature found links between medication non-adherence and higher spending (Cutler et al., 2018) and elevated risks of inpatient hospitalization and mortality (Walsh et al., 2019). To our knowledge, however, there have been limited studies examining the association between non-adherence and economic burden specific to nintedanib, antifibrotics, or idiopathic pulmonary fibrosis (IPF).

Measuring medication adherence is difficult. There are several approaches to measuring adherence, each with its own strengths and limitations (Forbes et al., 2018). A common method in real-world settings, such as prescription drug claims databases, is the proportion of days covered (PDC), which is defined for a specific medication as the number of days supplied divided by the total number of days in the study period (Anghel et al., 2019). Although PDC is useful in that it offers in a single number a metric of medication adherence over a predefined period, its simplicity masks any heterogeneity in adherence between patients and specifically does not capture changes in individual patient adherence over time.

An alternative approach is to use group-based trajectory modelling (GBTM) to detect trajectories of medication adherence over time and identify clusters of individuals who follow similar longitudinal adherence patterns (Nagin and Odgers, 2010). GBTM has been used to understand adherence to medications in several therapeutic areas (Alhazami et al., 2020). Longitudinal evaluation of medication adherence using GBTM can yield more informative classifications compared to traditional methods such as PDC (Franklin et al., 2013).

A prior study by this study team quantified nintedanib adherence trajectories using GBTMs and identified characteristics of patients associated with membership in each trajectory group. Individuals with idiopathic pulmonary fibrosis (IPF) who initiated nintedanib during 10/1/2014–12/31/2018 were identified in 100% Medicare claims and enrollment data. The sample consisted of community-dwelling older adults (≥66 years) with continuous coverage in Medicare Parts A, B and D for one year before (baseline) and after (follow-up) starting nintedanib. PDC was calculated for each of 12 consecutive 30-day months based on nintedanib claim fill dates and days' supply. PDC was dichotomized, with PDC ≥0.8 considered adherent. A series of GBTMs of adherence was estimated to identify the best-fitting specification. Patients were then grouped based on their estimated adherence trajectories. Associations between baseline patient characteristics, including demographics, comorbidities, and health case use, and group membership probabilities were quantified as odds ratios using fractional multinomial logit modelling.

In thas study, the best-fitting GBTM had five adherence trajectory groups: highly adherent (43.1%), medium adherent (11.9%), gradual decliners (10.4%), intermediate decliners (13.2%), and rapid decliners (21.5%) (Figure 1). The principal factors associated with higher odds of being in at least one of the lower-adherence groups were older age, female sex, race and ethnicity other than non-Hispanic white, and taking an additional medication during baseline.

A handful of existing studies examine associations between medication non-adherence as measured from GBTMs and coincident or subsequent health care resource use. Dillon et al. (2019) found lower GBTM-based adherence to antihypertensive medications was associated with a higher rate of visits to general practitioners but not hospitalizations in Ireland. Franklin et al. (2015) found lower GBTM-based adherence to statin medications was associated with higher risk of clinical events as measured by a composite of hospitalization for an acute coronary event, revascularization, a cerebrovascular event and heart failure in a large commercial insurance claims database in the United States. A pair of studies by Lo-Ciganic and colleagues used Medicaid claims data from Pennsylvania. They found lower GBTM-based adherence to buprenorphine led to higher risk of hospitalization and emergency department (ED) visits (Lo-Ciganic, Gellad, et al., 2016), and lower GBTM-based adherence to oral hypoglycemic medications led to higher risk of diabetes-related hospitalizations/ED visits.

This study seeks to fill the gap in knowledge about the potential association between adherence to nintedanib and patients' health care resource use and spending. We expect the findings from this study to be highly relevant to clinicians and payers to develop actionable strategies to improve adherence to nintedanib.

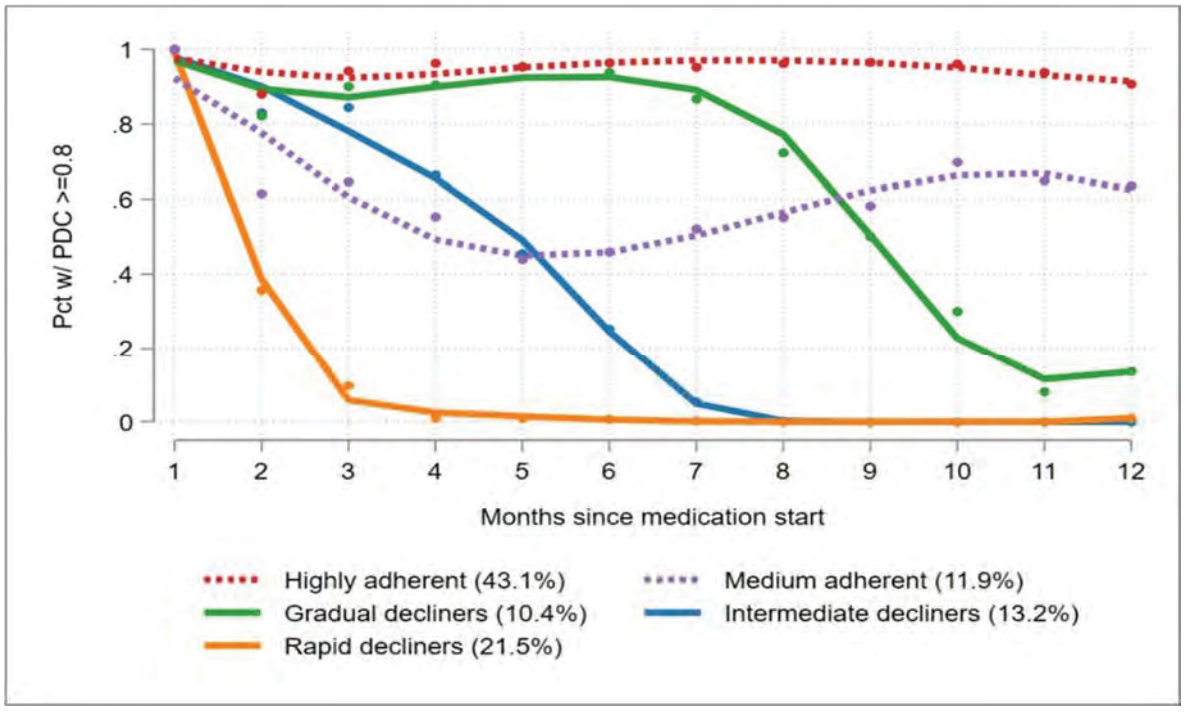

Figure 1. Nintedanib adherence trajectories

8. RESEARCH QUESTION AND OBJECTIVES

This study has two objectives:

1) To assess the association between nintedanib adherence trajectory group (as measured from a GBTM) and health care resource use, with a focus on inpatient hospitalization, among patients with IPF.
2) To assess the association between a patient's nintedanib adherence trajectory group (as measured from a GBTM) and their medical costs among patients with IPF.

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 2, 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 two-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 12/31/2020.

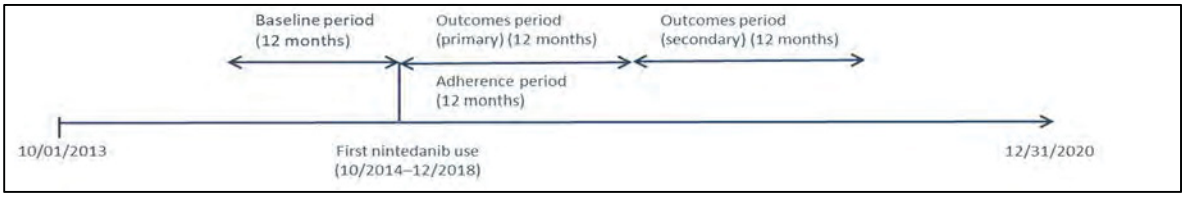

Figure 2. Study design schematic

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
  - 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 (≥14 days apart) with a diagnosis code for IPF (ICD-10-CM: J84.112; ICD-9-CM: 516.31) during the baseline period

- Exclusion criteria:
  - Had any history of pirfenidone or nintedanib use during the baseline period
  - Had any history of lung transplant during the baseline, index date or follow-up periods
  - 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

The exposure will be a categorical variable indicating which of the five nintedanib adherence trajectory groups a patient was most likely to belong, given their 12-month pattern of nintdanib claims as estimated from the GBTM. The groups (and their prevalence in the sample) are highly adherent (43.1%), medium adherent (11.9%), gradual decliners (10.4%), intermediate decliners (13.2%), and rapid decliners (21.5%).

9.3.2 Outcomes

The primary outcome will be total all-cause medical costs, which will be calculated as the sum of total amounts paid (by payers and patients) for all medical services. Types of medical services covered by Medicare include inpatient facility, outpatient facility, skilled nursing facility, home health care, hospice, durable medical equipment, and clinician office visits (and other services covered under the Part B benefit). This outcome will exclude spending on outpatient pharmacy (as covered under the Part D benefit).

The secondary outcomes will be:

1. Total IPF-related medical costs, which will be calculated as the sum of total amounts paid (by payers and patients) for all medical services for an IPF-related reason (at least one IPF diagnosis code).
2. All-cause inpatient hospitalization
3. IPF-related inpatient hospitalization.

9.3.3 Covariates

Study covariates are listed here and will be measured at the index date or during the 12 months prior.

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

Variable	Description
	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.
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 Robert Graham Center. 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

Variable	Description
	on their own. Moreover, unlike the Charlson and Elixhauser indexes, Gagne et al.'s (2011) combined index is not conditioned on inpatient hospital admission. 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.
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.
Asthma	A binary indicator for whether the beneficiary had a diagnosis code for asthma on at least one inpatient, outpatient or Carrier 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, outpatient or Carrier 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

Variable	Description
	least one inpatient, outpatient or Carrier 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, outpatient or Carrier 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, Carrier, skilled nursing facility, home health or durable medical 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, Carrier, 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, outpatient or Carrier 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, outpatient or Carrier 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, outpatient or Carrier 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 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

Variable	Description
	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 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.

Variable	Description
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.
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

Variable	Description
	ResDAC here. Thus, emergency department visits will be identified in inpatient and outpatient facility claims via the presence of revenue center codes 0450-0459 and 0981.
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.
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.

9.4 DATA SOURCES

The study will use data from the federal Medicare program on elderly beneficiaries consistently enrolled in traditional, or fee-for-service, Medicare insurance coverage for hospital (Part A), physician (Part B) and pharmacy (Part D) claims. As of October 2021, there were over 36 million beneficiaries in traditional Medicare. The study will focus on enrollment and claims data from October 1, 2013, through December 31, 2020. Access to these data has been obtained by [redacted] through the [redacted].

This data source was selected for multiple reasons. First, Medicare data capture the preponderance of IPF cases. In a study reported by Ipatova et al. (2019), 76% of patients on nintedanib or pirfenidone were ≥65 years of age. Second, Medicare claims are comprehensive in their inclusion of covered services, including outpatient prescription drugs (through Medicare Part D). Third, there is comparatively little turnover among Medicare beneficiaries compared with commercial insurance enrollees, which means that it is possible to follow Medicare beneficiaries for longer periods on average and more patients will qualify for a study requiring a given minimum continuous coverage period. Fourth, Medicare claims were used in the prior study of nintedanib adherence, so it is natural to continue using them for this study.

9.5 STUDY SIZE

In the prior study, there were 18,733 Medicare beneficiaries with at least one claim for nintedanib between 10/01/2014 and 12/31/2018. After sample selection criteria were applied, the final analytic sample consisted of 1,798 patients (**Figure 3**).

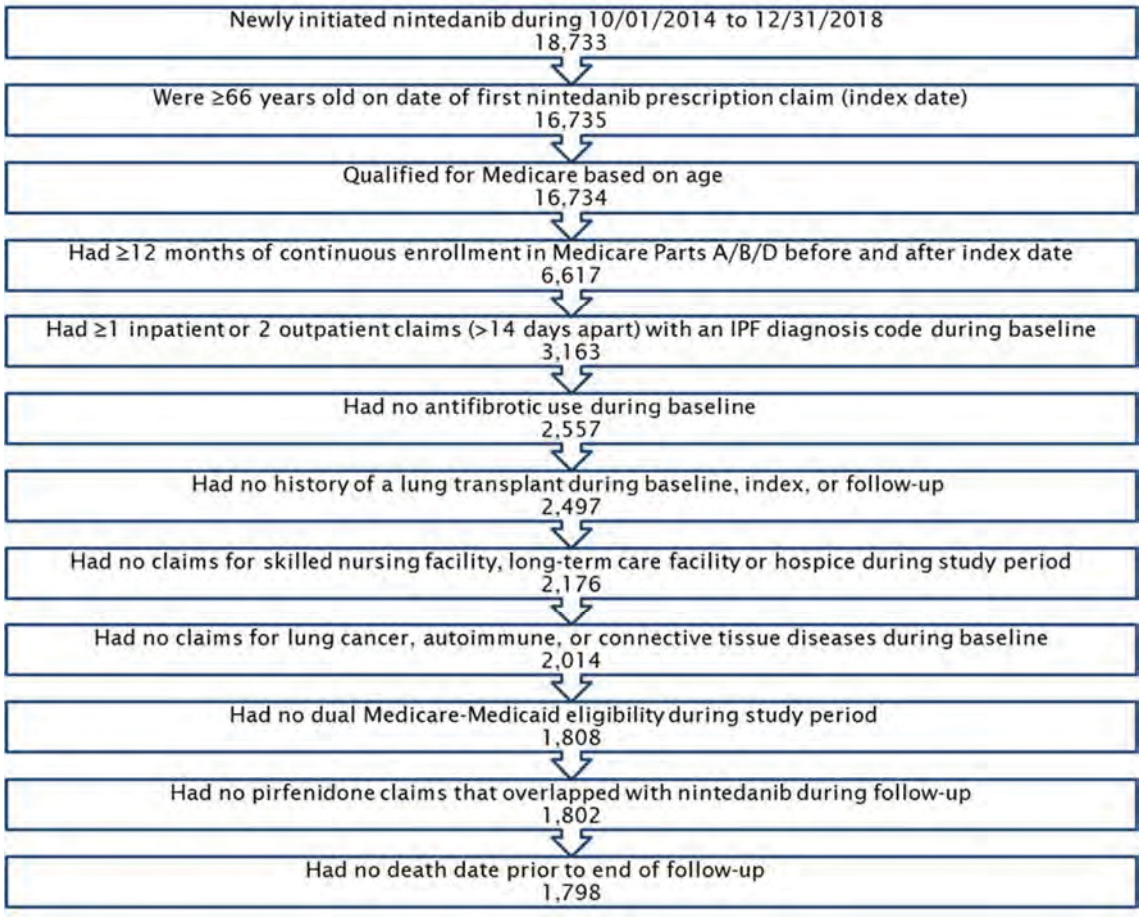

Figure 3. Sample selection in the prior study of nintedanib adherence trajectories

9.6 DATA MANAGEMENT

Data manipulation and analysis will be conducted by [redacted]. Pursuant to requirements guiding participation in the [redacted] Innovator program, [redacted] staff will access the Medicare claims and enrollment 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.

Data security will be assured along two dimensions. First, the data will reside only in [redacted] secure [redacted] environment. [redacted] staff have completed a rigorous identity verification process to gain access to the [redacted]. [redacted] prohibits any patient-level data from

being copied from the [redacted]; only aggregated data based on at least 11 patients is allowable. Second, only a limited set of patient identifiers will be present in the data, including residential ZIP Code and full dates of health insurance enrollment and claims and subject's birth and death dates. The unique patient ID used by [redacted] is a synthetic identifier, and no [redacted] study staff will have access to the linking file to real subject identifiers.

Additionally, study documents, including synopsis, protocol, and final results as well as publications, will be archived on the [redacted] Team site.

9.7 DATA ANALYSIS

9.7.1 Main analysis

Descriptive statistics of the covariates will be calculated stratified by the five categories of patients' adherence trajectory group membership, after assigning patients to the group for which they had the highest posterior probability of membership as estimated in the GBTM (from the prior study). Tests of joint equality across groups will be computed using ANOVA and nonparametric Kruskal-Wallis rank tests for continuous measures and χ^2 tests for categorical measures.

Mean outcomes will be compared between pairs of nintedanib adherence trajectory membership categories (referent group: highly adherent) using a regression modeling framework. Unadjusted means will be compared first using an "empty" linear regression model specification (with no covariates or weights) that makes standard errors robust to heteroskedasticity of unknown form. Adjusted means will then be compared using a "doubly robust" generalized linear model (GLM) specification that also uses heteroskedasticity-robust standard errors. More detail about the double-robustness is provided below.

The functional form of the GLM will be selected for each outcome based on its observed distribution in the data. The binary outcome of "any hospitalization" will likely be modeled with logistic regression. The non-negative "total LOS" outcome may be modeled with a quasi-maximum likelihood Poisson model if the proportion of patients with zero days of hospitalization is sufficiently low (less than 10%), or a two-part model (e.g., logistic model of any hospitalization vs. none and a simultaneously estimated Poisson model of total LOS conditional on having positive LOS) if not (Belotti et al., 2015). Similarly, if the "total medical costs" outcome has a pile-up at zero, a two-part model will be estimated; if not, a GLM with a log link and a distribution family decided by application of the modified Park test will be estimated (Manning, 1998).

Potential confounding by observed covariates will be addressed in two ways, thus leading to "doubly robust" estimates. The first way is to calculate two sets of observation-level weights that balance covariates across exposure categories: inverse probability of treatment weights (IPTWs) and weights derived from a marginal mean weighting through stratification (MMWS) procedure (Hong, 2012; Linden, 2014). To generate the weights, a multinomial logit model of nintedanib adherence trajectory group category will be estimated as a function of the covariate roster. Predicted probabilities (i.e., propensity scores) for each category will be generated from the model results and used to calculate both the IPTW and MMWS

weights. Because multiple exposure categories are to be compared, the weights will provide estimates of the average treatment effect (ATE) (and not the average treatment effect on the treated [ATT]).

The second way confounding will be addressed is through regression adjustment; that is, observed covariates will be added to the GLM specification. Combining weighting with regression adjustment yields a double robustness property that attenuates bias in the case when either the treatment model (i.e., the multinomial logit model of exposure category) or the outcome model (i.e., the GLM of the health care resource use or spending outcome) is misspecified (Linden et al., 2016).

To facilitate interpretability, the regression model results will be transformed back to the scale of the outcome variable. Average marginal effects and their 95% confidence intervals (CIs) will be calculated using the delta method. Data preparation will be performed using SAS 9.4 ( ) and data analysis will be conducted using Stata 17 ( ).

[redacted]

9.8 QUALITY CONTROL

Regarding quality control procedures around the data, the Medicare administrative data collection occurred in the past and access to the data is being provided by . No additional insight into the data collection procedures is available beyond that which has been published by . As a result, we are relying on quality control measures implemented by during data collection.

Regarding quality control procedures around the analyses, the following quality assurance and quality control measures will be applied to all programming that executes data extraction and transformation by

- 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

The study has several limitations, including:

- The data source consists of administrative claims data, which do not include important determinants of health care resource use and cost outcomes that may be correlated with the adherence exposure, such as IPF disease severity.
- Although the outcomes should be measured accurately, the adherence exposure is necessarily based on prescription fill data from claims and may mismeasure actual nintedanib use.
- Sample selection bias may arise from the design decision to exclude patients who do not have at least 12 months of follow-up data after nintedanib initiation for primary outcomes (and 24 months for secondary outcomes).
- Generalizability may be limited to IPF patients who are continuously covered under fee-for-service Medicare, including Parts A, B and D.

9.10 OTHER ASPECTS

9.10.1 Ethical Approval

Although these data are not de-identified, pursuant to [redacted] requirements, this research study has been determined to be exempt from institutional review board (IRB) review and has been granted a full waiver of HIPAA authorization for use and disclosure of protected health information by the WCG Institutional Review Board.

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 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 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. ANNEXES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. 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

Study Title: Economic burden associated with nintedanib non-adherence among Medicare beneficiaries with IPF

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.

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: _____

APPROVAL / SIGNATURE PAGE

Document Number: c42255024 **Technical Version Number:2.0**

Document Name: nis-protocol-nintedanib-v3

Title: Economic burden associated with nintedanib non-adherence among Medicare beneficiaries with IPF

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval	[redacted]	25 May 2023 15:46 CEST
Approval		25 May 2023 15:58 CEST
Approval		25 May 2023 16:02 CEST
Approval		25 May 2023 16:12 CEST
Approval		25 May 2023 16:53 CEST
Approval-Team Member Medical Affairs		02 Jun 2023 09:33 CEST
Approval-Team Member Drug Safety		09 Jul 2023 21:11 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed