Protocol for non-interventional studies based on existing data

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2. LIST OF ABBREVIATIONS

ACR	Albumin to creatinine ratio
ALP	Alkaline phosphatase
ALT	Alanine transaminase
APTT	Activated partial thromboplastin time
ASD	Absolute standardized differences
AST	Aspartate transaminase
BMI	Body mass index
BP	Blood pressure
CCI	Charlson comorbidity index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DCCO	Diffusing capacity of carbon monoxide
EMR	Electronic medical records
ER	Emergency room
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
GERD	Gastroesophageal reflux disease
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transpeptidase
HDL	High-density lipoprotein
HIPPA	Health Insurance Portability and Accountability Act
HRCT	High resolution computed tomography
ICD-9-CM	The International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	The International Classification of Diseases, Tenth Revision, Clinical Modification
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
IRB	Institutional Review Board
LDL	Low-density lipoprotein
OTC	Over-the-counter
PFT	Pulmonary function test
PS	Propensity score
PT	Prothrombin time
ROC	Receiver operating characteristic
SD	Standard deviation
SLB	Surgical lung biopsy
TLC	Total lung capacity

3. RESPONSIBLE PARTIES

Principal investigator:

Other investigators:

4. ABSTRACT

Name of company: Boehringer Ingelheim (BI)			
Name of finished medicinal product: Ofev (BI)			
Name of active ingredient: Nintedanib			
Protocol date: 18 December 2018	**Study number:**	**Version/Revision:** 1.0	**Version/Revision date:** 18 December 2018
Title of study:	Characteristics of IPF patients initiating nintedanib, pirfenidone or no antifibrotic treatment in the US		
Rationale and background:	Idiopathic Pulmonary Fibrosis (IPF) is a debilitating, life limiting condition with a median survival range of 2.5 to 3.5 years from the time of diagnosis and an estimated incidence of 6.8-16.3 per 100,000 persons. Despite its rarity, the economic burden of IPF is significant, with the annual medical cost to the US healthcare system estimated at close to $2 billion in 2012. The goals of treatment for IPF are to stop disease progression, reduce symptoms, prevent acute exacerbations, and prolong survival. The treatment options for IPF were limited until the FDA approved two products in October 2014, Ofev (nintedanib, BI) and Esbriet (pirfenidone, Genentech), that slowed disease progression. BI is interested in conducting research to understand differences in characteristics of patients who are prescribed these two drugs, and those who do not receive a prescription for an antifibrotic treatment.		
Research question and objectives:	To understand characteristics of patients treated with nintedanib and pirfenidone, as well as patients who do not receive a prescription for an antifibrotic treatment. The primary objective is: 1. To describe and compare demographic, clinical, and other characteristics of IPF patients initiating nintedanib, pirfenidone, or not receiving prescription antifibrotic treatment The secondary objective is: 2. To compare and contrast the probability of receiving nintedanib vs. pirfenidone and nintedanib or pirfenidone vs. untreated in IPF patients using baseline patient characteristics		
Study design:	A retrospective cohort database study		
Population:	This study will use data from GE Centricity electronic medical records (EMR) database obtained from a national network of primary care practices in the US. The study population will include patients (≥ 40 years old) with ≥ 1 diagnosis of IPF in EMR records and newly prescribed nintedanib or pirfenidone or patients with no prescription for		

	antifibrotic treatment between October 1, 2014 and April 30, 2018. Patients will be divided into three mutually exclusive cohorts: (1) nintedanib initiators; (2) pirfenidone initiators; and (3) control cohort who received no prescription antifibrotic treatment during selection window.
Variables:	The following demographic and clinical characteristics as well as medical interventions for IPF during the 12-month baseline period (pre-treatment) will be evaluated and compared between cohorts • Demographic characteristics (e.g., age, gender, race/ethnicity, geographic region, insurance type) • Clinical characteristics (e.g., selected comorbidities, baseline weight and body mass index [BMI], blood pressure, smoking status, laboratory measures, pulmonary function tests) • Pharmacological interventions (e.g., index medication dose, time from the earliest diagnosis of IPF to index medication, other IPF treatments, bronchodilators, corticosteroids) • Non-pharmacological interventions (e.g., surgical procedures, supportive therapies, diagnostic procedures)
Data sources:	GE Centricity EMR database from October 2013 to April 2018
Study size:	A preliminary analysis identified 868 IPF patients with pirfenidone, 615 patients with nintedanib, and about 10,000 untreated patients.
Data analysis:	Patient demographic and clinical characteristics will be described using descriptive analyses. Counts and percentages for categorical variables and measures of central tendency (mean, median, standard deviation [SD], and min/max) for continuous variables will be reported. Differences between the treatment cohorts (compared to each other and to untreated patients) will be assessed using absolute standardized differences and p-values. The probabilities of receiving one treatment over another will be tested by propensity scores and using multivariable logistic regression adjusted for key baseline characteristics. The similarities and differences between two treatment cohorts will be assessed using balance diagnostics tests. A stratified descriptive analysis will also be conducted at different time points to assess if the characteristics of the two exposures changes over time.
Milestones:	**Milestone** / **Planned Date** Start of data collection / December 2018 (start of data analysis) End of data collection / March 2019 (end of data analysis) Preliminary results / January/February 2019 Final report of study results / June 2019

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
Start of data collection	December 2018 (start of data analysis)
End of data collection	March 2019 (end of data analysis)
Preliminary results	January/February 2019
Final report of study results	June 2019

7. RATIONALE AND BACKGROUND

Idiopathic Pulmonary Fibrosis (IPF) is a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, and limited to the lungs.[1] IPF is a debilitating, life limiting condition with a median survival range of 2.5 to 3.5 years from the time of diagnosis.[2] A study using insurance claims data from the United States estimated the incidence of IPF to be between 6.8 and 16.3 per 100,000 persons.[3] The same study yielded a prevalence estimate of between 14.0 and 42.7 per 100,000 persons, depending on the case definition used.[3] The economic burden of IPF is significant, with the annual medical cost (hospitalization, emergency room [ER] visits, outpatient visits, and use of procedures and tests) to the US healthcare system estimated at close to $2 billion in 2012.[4]

The goals of treatment for IPF are to stop disease progression, reduce symptoms, prevent acute exacerbations, and prolong survival.[5] Pulmonary rehabilitation and oxygen treatment are commonly utilized as supportive treatments, and lung transplant surgery may be considered in some patients.[5] Many pharmacological treatments (i.e. anticoagulants, combination of N-acetylcysteine, prednisone and azathioprine, selective endothelin receptor) have been evaluated in IPF patients; however, international guidelines recommend against the use of these treatments due to insufficient evidence.[6] The treatment options for patients with IPF changed significantly in October 2014 when the FDA approved two products that slowed disease progression, Ofev (nintedanib, Boehringer Ingelheim) and Esbriet (pirfenidone, Genentech).[7,8] Recently updated American Thoracic Society/European Respiratory Society/Japanese Respiratory Society, and Latin American Thoracic Association clinical practice guidelines gave conditional recommendations for the use of nintedanib and pirfenidone in the majority of patients with IPF.[6]

Several clinical trials have been conducted to evaluate the efficacy and safety of these two emerging treatments. A recent systematic review and meta-analysis of ten randomized controlled trials showed that both pirfenidone and nintedanib reduced the progression of IPF in terms of FVC (forced vital capacity) decline and had similar safety profiles.[9] However, only nintedanib significantly reduced the risk of all-cause and respiratory death. Pirfenidone and nintedanib also reduced the risk of a ≥10% decline in FVC over 12 months, although only nintedanib protected against the risk of acute exacerbations.[9]

Patients selected into clinical trials usually present with fewer comorbidities, fall between certain age limits, and the severity of their disease is defined.[10] Therefore, clinical trial populations do not always reflect the entire population affected by IPF in the real-world setting. Understanding patient characteristics is essential when assessing the real-world effectiveness of a treatment. Unlike being randomly assigned to a treatment in clinical trials, patients in the real world may choose between similar treatments based on existing comorbidities and concomitant medications, differentiating the effectiveness of the medications in certain patients. When comparing nintedanib and pirfenidone, it is therefore important to understand the differences in clinical characteristics of patients who are prescribed nintedanib compared to patients who are prescribed pirfenidone, and how these patients compare to IPF patients who do not receive antifibrotic treatment.

In order to help identify the profile of patients and specific characteristics associated with initiating treatment for IPF, BI is conducting a retrospective database study to understand differences in characteristics of patients who are prescribed pirfenidone or nintedanib, and those who do not receive a prescription for an antifibrotic treatment. This study will also help identify patient characteristics driving the initiation of nintedanib or pirfenidone by assessing the probability of receiving the treatments.

8. RESEARCH QUESTION AND OBJECTIVES

The overall aim of this retrospective database study is to understand differences in characteristics of IPF patients who are prescribed nintedanib compared to those who are prescribed pirfenidone, and how these patients compare to patients who do not receive a prescription for antifibrotic treatment.

The primary objective is:

1. To describe and compare demographic, clinical, and other characteristics of IPF patients initiating nintedanib, pirfenidone, or not receiving prescription antifibrotic treatment

The secondary objective is:

2. To compare and contrast the probability (by propensity score) of receiving nintedanib vs. pirfenidone and nintedanib or pirfenidone vs. no treatment in IPF patients using baseline patient characteristics

9. RESEARCH METHODS

9.1 STUDY DESIGN

To address the objectives above, this retrospective database study will use a new user cohort design, where cohorts are defined based on the exposures of interest (i.e., prescription for nintedanib or pirfenidone or no antifibrotic treatment). The study population will consist of the following three mutually exclusive cohorts:

1. Nintedanib initiators, consisting of adult IPF patients who newly initiated nintedanib treatment
2. Pirfenidone initiators, consisting of adult IPF patients who newly initiated pirfenidone treatment
3. Untreated cohort, consisting of adult IPF patients without any prescription for antifibrotic treatment (i.e., no prescription for nintedanib nor pirfenidone)

The primary study endpoint is the absolute standardized differences (ASD) and p-value comparing patient characteristics between the two treatment cohorts and between each treatment cohort and the untreated cohort, where an ASD of at least 10% will be considered a meaningful difference. The secondary endpoint is the probability (estimated using propensity score) of receiving nintedanib vs. pirfenidone and that of receiving nintedanib or pirfenidone vs. no treatment based on patient characteristics; to identify baseline characteristics that drive initiation of a treatment while minimizing prescription bias.

These analyses will utilize real-world data to understand differences in patient characteristics between those prescribed nintedanib versus pirfenidone and those not receiving any antifibrotic treatments. The proposed data source, EMR data, allows exploration of several clinical characteristics (e.g., laboratory measures, medications, behavioral measures) in patients with IPF in a setting outside of a clinical trial.

9.2 SETTING

This retrospective database study will leverage the GE EMR data from October 1, 2013 to April 30, 2018. The EMR consists of patient data from ambulatory care records in the US and is representative of the US population receiving healthcare in the ambulatory setting. Patients will be included in one of three study cohorts based on prescription history from October 1, 2014 to April 30, 2018, allowing for a 12-month pre-index period to describe patient demographic, clinical and treatment characteristics.

Index date

The index date for the nintedanib (or pirfenidone) cohort will be the date of the first nintedanib (or pirfenidone) prescription during the selection window (from October 1, 2014 to April 30, 2018). The index date for the untreated cohort will be the date of the earliest IPF diagnosis or a randomly assigned date between October 1, 2013 and April 30, 2018.

Pre-index period

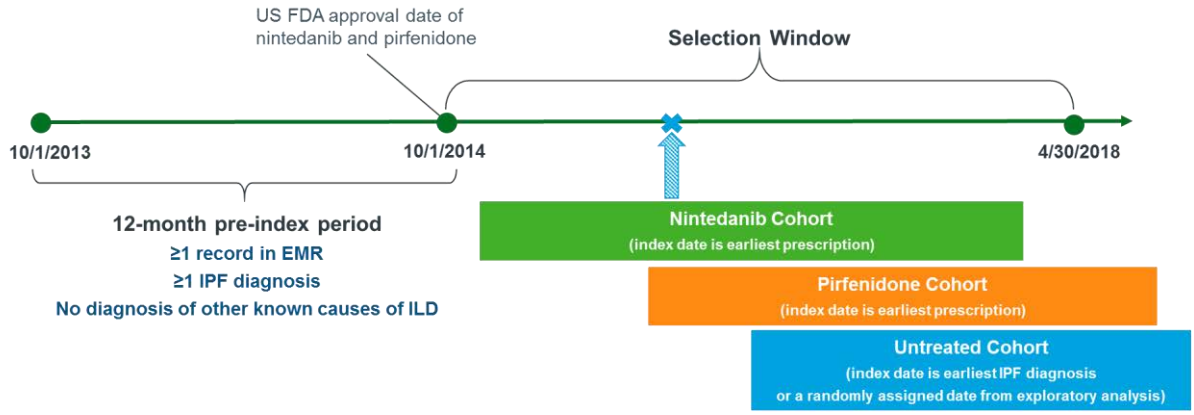
The pre-index period for each cohort will be the 12 months prior to the index date. Patients will be required to have ≥ 1 diagnosis of IPF during the pre-index period (see additional inclusion criteria described below).

Post-index period

The post-index period for each cohort will start from the index date. Since the study aims to evaluate patient characteristics during the pre-index period, no minimum follow-up will be required for post-index period and no study measures will be assess during the post-index period.

Patient selection is illustrated in Figure 1.

Figure 1. Patient Selection



Nintedanib cohort

Inclusion criteria:

- With ≥ 1 diagnosis for IPF (the International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 516.3, 516.31, 515,[11] or ICD-10-CM codes J84.112) in the EMR between October 1, 2013 to April 30, 2018
- With ≥ 1 prescription for nintedanib between October 1, 2014 and April 30, 2018 (the selection window)
  - The date of the first prescription will be defined as the index date
- With ≥ 1 record in the EMR database during the 12 months prior to the index date (the pre-index period)
- With ≥ 1 diagnosis of IPF during the 12 months prior to the index date
- Age ≥ 40 on the index date
- will explore also requiring ≥ 1 chest CT scan before first IPF diagnosis during the pre-index period[12]

Exclusion criteria:

- With ≥ 1 diagnosis of other known causes of interstitial lung disease (ILD) on the date of or after the first IPF diagnosis during the pre-index period[12,13]

  - Other known causes of ILD include conditions such as systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, Sjögren disease, and hypersensitivity pneumonitis (ICD-9-CM codes 135, 237.7, 272.7, 277.3, 277.8, 446.21, 446.4, 495, 500–505, 506.4, 508.1, 508.8, 516.0, 516.1, 516.32–516.37, 516.2, 516.8, 516.9, 517.0, 517.2, 517.8, 518.3, 555, 710.0, 710.0–710.4, 714.0, 714.81, 720, and 759.5, or ICD-10-CM equivalent codes)[12,13]
- With ≥ 1 prescription for nintedanib prior to the index date
- With ≥ 1 prescription for pirfenidone prior to or on the index date

Pirfenidone cohort

Inclusion criteria:
- With ≥ 1 diagnosis for IPF (ICD-9-CM codes 516.3, 516.31, 515,[11] or ICD-10-CM codes J84.112) in the EMR between October 1, 2013 to April 30, 2018
- With ≥ 1 prescription for pirfenidone between October 1, 2014 and April 30, 2018 (the selection window)
  - The date of the first prescription will be defined as the index date
- With ≥ 1 record in the EMR database during the 12 months prior to the index date
- With ≥ 1 diagnosis of IPF during the 12 months prior to the index date
- Age ≥ 40 on the index date
- will explore also requiring ≥ 1 chest CT scan before first IPF diagnosis during the pre-index period[12]

Exclusion criteria:
- With ≥ 1 diagnosis of other known causes of interstitial lung disease (ILD) on the date of or after the first IPF diagnosis during the pre-index period[12,13]
  - Other known causes of ILD include conditions such as systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, Sjögren disease, and hypersensitivity pneumonitis (ICD-9-CM codes 135, 237.7, 272.7, 277.3, 277.8, 446.21, 446.4, 495, 500–505, 506.4, 508.1, 508.8, 516.0, 516.1, 516.32–516.37, 516.2, 516.8, 516.9, 517.0, 517.2, 517.8, 518.3, 555, 710.0, 710.0–710.4, 714.0, 714.81, 720, and 759.5, or ICD-10-CM equivalent codes) [12,13]
- ≥ 1 prescription for pirfenidone prior to the index date
- ≥ 1 prescription for nintedanib prior to or on the index date

Untreated cohort

Inclusion criteria:
- With ≥ 1 diagnosis for IPF (ICD-9-CM codes 516.3, 516.31, 515,[11] or ICD-10-CM codes J84.112) in the EMR between October 1, 2013 to April 30, 2018
  - Index date will be defined as the date of the earliest IPF diagnosis or a randomly assigned date based on the exploratory analyses to be performed on the two treatment cohorts (exploring time from IPF diagnosis to treatment initiation)
    - will explore requiring ≥ 2 diagnoses for IPF that are ≥ 30 days apart to improve the identification of IPF patients[12,13]
- With ≥ 1 record in the EMR database during the 12 months prior to the index date (the pre-index period)

- Age ≥ 40 on the index date
- will explore also requiring ≥ 1 chest CT scan before first IPF diagnosis during the pre-index period[12]

Exclusion criteria:

- With ≥ 1 diagnosis of other known causes of interstitial lung disease (ILD) on the date of or after the first IPF diagnosis during the pre-index period
  - Other known causes of ILD include conditions such as systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis, polymyositis, Sjögren disease, and hypersensitivity pneumonitis (ICD-9-CM codes 135, 237.7, 272.7, 277.3, 277.8, 446.21, 446.4, 495, 500–505, 506.4, 508.1, 508.8, 516.0, 516.1, 516.32–516.37, 516.2, 516.8, 516.9, 517.0, 517.2, 517.8, 518.3, 555, 710.0, 710.0–710.4, 714.0, 714.81, 720, and 759.5, or ICD-10-CM equivalent codes) [12,13]
- With prescription for nintedanib or pirfenidone anytime during the data window

9.3 VARIABLES

9.3.1 Exposures

Both nintedanib (Ofev, BI) and pirfenidone (Esbriet, Genentech) were approved by the US FDA on October 15, 2014 (reflected by start of selection window in this study). Nintedanib initiators will be identified using prescription records for nintedanib, with the index date being the first prescription in the EMR during the selection window. Similarly, pirfenidone initiators will be identified using prescription records for pirfenidone; index date is first prescription. New users of these medications will be selected into the study, excluding those who initiated both medications on index. The number of patients who initiated both medications on index will be reported during the patient attrition. Since the purpose of this study is to identify predictors of IPF treatment initiation, no post-index follow-up measures will be reported. Patients who switched between the treatments during the pre-index period will be excluded because of the new user design, and those who switch after the index date will not be a concern as no study measures will be evaluated during the post-index period for the objectives of this study. No validation will be performed on the exposures of interest as exposure ascertainment relies on evidence of ≥ 1 prescription record.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary outcome will be the ASD and p-value comparing baseline patient characteristics (as described in section 9.3.3) between the following cohorts:

- Nintedanib vs. pirfenidone
- Nintedanib vs. untreated
- Pirfenidone vs. untreated

9.3.2.2 Secondary outcomes

The secondary outcomes will be the probabilities (propensity scores) of receiving one treatment over another (or probability of receiving antifibrotic treatment) between the following cohorts:

- Nintedanib vs. pirfenidone
- Treated patients (i.e., nintedanib or pirfenidone) vs. untreated

9.3.2.3 Further outcomes

None.

9.3.3 Covariates

The following measures will be evaluated during the 12-month baseline period, including index date, unless otherwise noted. Measures will be reported separately for each of the three cohorts.

For nintedanib and pirfenidone cohorts only:

- Index medication (n, %)
  - Nintedanib
  - Pirfenidone
- Average daily dose of the index prescription
  - Nintedanib (mean, SD, median, min, max) and categories (n, %)
    - 100 mg
    - 150 mg
    - Unknown
  - Pirfenidone (mean, SD, median, min, max) and categories (n, %)
    - 267 mg
    - Unknown
- Time from the earliest diagnosis for IPF to index (mean, SD, median, min, max)
- Prescribing physician specialty (n, %)
  - Primary care
  - Internal medicine
  - Pulmonologist
  - Other

For all cohorts:

Demographic characteristics

- Age (mean, SD, median, min, max) and age categories on index date (n, %)
  - 40-49
  - 50-59

  - 60-69
  - ≥70
- Gender (n, %)
  - Male
  - Female
- Index year (n, %)
  - 2014
  - 2015
  - 2016
  - 2017
  - 2018
- Region (n, %)
  - Northeast
  - Midwest
  - South
  - West
- Race/ethnicity (n, %) (expected to be missing for about 40% of patients)
  - White
  - African American
  - Hispanic
  - Asian
  - Other
  - Unknown
- Payer type (n, %)
  - Commercial
  - Medicaid
  - Medicare
  - Self-Insured
  - Other/Unknown

Clinical characteristics (based on ICD-9/10-CM procedure and diagnosis codes, laboratory test codes, CPT codes and NDC/RxNorm (to be included in Appendix), as well as other information in the EMR encounter files)

  - Body weight (lbs; mean, SD, median, min, max)
  - Body mass index (BMI; kg/m^2; mean, SD, median, min, max)
  - BMI category, defined using BMI field (n, %)
    - Underweight (<18.5 kg/m^2)
    - Normal weight (18.5 to 24.99 kg/m^2)
    - Overweight (25 to 29.99 kg/m^2)
    - Obese (30 to 34.99 kg/m^2)
    - Very obese (≥ 35 kg/m^2)

- Blood pressure (BP)[14] (n, %)
  - Diastolic BP
    - Normal (<80 mmHg)
    - High (≥80 mmHg)
  - Systolic BP
    - Normal (<120 mmHg)
    - Elevated (≥120 and < 129 mmHg)
    - High (≥130 mmHg), further broken down as follows if data allow
      - Stage 1 (≥130 and < 139 mmHg)
      - Stage 2 (≥140 mmHg)
- Smoking status at index (n, %); excluding smokeless tobacco; categories to be finalized during analysis
  - Smoker
  - Non-smoker, further broken down as follows if data allow
    - Previous smoker
    - Never smoker
  - Unknown/missing
- Alcohol consumption (n, %)
  - Yes
  - No
  - Unknown/missing
- Charlson comorbidity index (CCI) [15] (mean, SD, median, min, max) and categories (n, %), defined using ICD diagnosis codes
  - 0
  - 1
  - 2
  - 3
  - 4+
- Respiratory comorbidities[16] (n, %), defined using ICD diagnosis codes
  - COPD (Chronic obstructive pulmonary disease), includes chronic bronchitis and emphysema
  - Pulmonary hypertension
  - Obstructive sleep apnea
  - Lung cancer
  - Pulmonary embolism
  - Asthma
  - Acute respiratory distress syndrome
  - Pulmonary edema
  - Cough
  - Upper respiratory tract infection (includes acute bronchitis)
  - Bronchitis (not specified as acute or chronic)

        - Sinusitis
    - Gastroesophageal reflux disease (GERD) (n, %), defined using ICD diagnosis codes
    - Metabolic disorders[16] (n, %), defined using ICD diagnosis codes
        - Obesity (defined as ICD-9 code 278.0 or ICD-10 code E66 or BMI ≥ 30 kg/m^2)
        - Diabetes
            - Any diabetes
            - Type 1 diabetes
            - Type 2 diabetes[16]
        - Dyslipidemia (includes hypercholesterolemia and hyperlipidemia)
    - Cardiovascular disorders[16] (n, %), defined using ICD diagnosis codes
        - Arrhythmia
        - Atrial fibrillation
        - Heart failure
        - Ischemic heart disease
        - Stroke
        - Hypertension (includes systemic arterial hypertension)
        - Peripheral arterial diseases
        - Cardiomyopathy
    - Mental disorders (n, %), defined using ICD diagnosis codes
        - Depression
        - Anxiety
        - Schizophrenia
        - Dementia
        - Bipolar disorders
    - Renal impairment (n, %), defined using ICD diagnosis codes
    - Hepatic impairment (n, %), defined using ICD diagnosis codes

- Laboratory measures (to the extent that the data allow; tests will be identified by procedure codes and EMR data fields; if repeated measurements of a test are observed, the one closest to the index date will be reported, with the exception of several renal and liver measures (where noted) when any evidence of patient history of the condition during baseline will take precedent over the measure closest to index)
    - Anticoagulation tests (n, %)
        - Prothrombin time (n, %)
            - High (>14 seconds)
            - Normal (10-14 seconds)
            - Low (<10 seconds)
        - Activated partial thromboplastin time (aPTT; n, %)
            - Normal (30-40 seconds)
            - Elevated (41-70 seconds)

        - Critical (>70 seconds)
    - Bleeding time (n, %)
        - Normal (1-9 minutes)
        - Platelet dysfunction (10-15 minutes)
        - Critical (>15 minutes)
- Hematologic markers
    - Blood hemoglobin (mean, SD, median, min, max)
    - Blood hematocrit (mean, SD, median, min, max)
    - Red blood cell count (mean, SD, median, min, max)
    - Platelet count (n, %)
        - Low (<150,000 platelets/mcL)
        - Normal (150,000-450,000 platelets/mcL)
        - High (>450,000 platelets/mcL)
    - Conventional C - reactive protein (n, %)
        - Normal (≤5.0 mg/L)
        - High (>5.0 mg/L)
- Liver function tests (n, %)
    - Alanine transaminase (ALT; n, %); patient history of high ALT level suggesting hepatic impairment will be reported and take precedent to ALT value closest to index
        - Low (<7 U/L)
        - Normal (7 – 56 U/L)
        - High (>56 U/L)
    - Aspartate transaminase (AST; n, %); patient history of high AST level suggesting hepatic impairment will be reported and take precedent to AST value closest to index
        - Low (<5 U/L)
        - Normal (5 – 40 U/L)
        - High (>40 U/L)
    - Alkaline phosphatase (ALP; n, %)
        - Low (<44 IU/L)
        - Normal (44 – 147 IU/L)
        - High (>147 IU/L)
    - Gamma-glutamyl transpeptidase (GGT; n, %)
        - Low (<9 U/L)
        - Normal (9-48 U/L)
        - High (>48 U/L)
    - Total bilirubin (n, %); patient history of high bilirubin level suggesting hepatic impairment will be reported and take precedent to value closest to index
        - Low (<0.2 mg/dL)

        - Normal (0.2-1.2 mg/dL)
        - High (>1.2 mg/dL)
    - Kidney function tests (n, %)
        - Albumin to creatinine ratio (ACR; n, %)
            - Normal (<30)
            - Microalbuminuria (30-300)
            - Macroalbuminuria (>300)
        - Glomerular filtration rate (GFR; n, %); patient history of low GFR suggesting renal impairment will be reported and take precedent to value closest to index
            - Low (<90 mL/min/1.73m^2)
            - Normal (90 – 120 mL/min/1.73m^2)
            - High (>120 mL/min/1.73m^2)
        - Serum creatinine (mean, SD, median, min, max); patient history of high serum creatinine level suggesting renal impairment will be reported and take precedent to value closest to index
    - Cholesterol levels (n, %)
        - Total cholesterol (mg/dL; n, %)
            - Normal (<200 mg/dL)
            - Borderline high (200-239 mg/dL)
            - High (≥240 mg/dL)
        - Triglyceride (mg/dL; n, %)
            - Normal (<150 mg/dL)
            - Borderline high (150-199 mg/dL)
            - High (≥200 mg/dL)
        - Cholesterol in high-density lipoprotein (HDL; n, %)
            - Normal (≥40 mg/dL)
            - Abnormal (<40 mg/dL)
        - Cholesterol in low-density lipoprotein (LDL; n, %)
            - Normal (<100 mg/dL)
            - Borderline high (100 – 159 mg/dL)
            - High (≥160 mg/dL)
- Pulmonary function tests (PFTs) indicative of IPF severity (n, %)
    - FVC (n, %)
        - Normal (≥80%)
        - Abnormal (<80%)
    - Forced expiratory volume in one second (FEV1) /FVC ratio (n, %)
        - Normal (≥70%)
        - Abnormal (<70%)
    - Total lung capacity (TLC) (mean, SD, median, min, max)
    - Carbon monoxide diffusing capacity of the lung (DLCO; n, %)

        - Normal (>75% of predicted)
        - Mild to moderate decrease (40-74% of predicted)
        - Severe decrease (<40% of predicted)
    - Oxygen saturation (n, %)
        - Normal (95-100%)
        - Below normal (<95%)
    - GAP index[18] (n, %), if data allow
        - Calculated using information on age, gender and FVC
        - Stage I (0-3 points)
        - Stage II (4-5 points)
        - Stage III (6-8 points)

Treatment history during the pre-index period (not including index date):

- Pharmacological interventions (n, %)
    - Other treatments (as per ATS/ERS/JRS/ALAT guidelines[19])
        - Selective tyrosine kinase inhibitor against platelet derived growth factor (Imatinib)
        - Prednisone
        - Azathioprine
        - N-acetylcysteine
        - Selective endothelin receptor antagonist (ambrisentan)
        - Phosphodiesterase-5 inhibitor (sildenafil)
        - Dual endothelin receptor antagonists (macitentan, bosentan)
    - Corticosteroids
        - Inhaled corticosteroids
        - Oral corticosteroids
    - Bronchodilators
        - SABA
        - LABA
        - Anticholinergics
        - Other beta agonists
    - GERD therapy
        - H-2 receptor blockers
        - Proton pump inhibitors
        - Antacids
    - Cardiovascular drugs
        - Antianginals
        - Antihypertensives
        - Antiarrhythmics
        - Antiplatelets
        - Anticoagulants

- Antidiabetes drugs
- Anti-infectives
- Anticonvulsants
- Anti-anxiety drugs
- Antidepressants
- Antipsychotics
- Antihyperlipidemics

- Non-pharmacological interventions (n, %)
  - Surgical procedures (n, %)
    - Lung transplantation
    - Esophageal sphincter reinforcement
    - Lung cancer surgeries
  - Supportive therapy (n, %)
    - Oxygen therapy
    - Pulmonary rehabilitation
  - Diagnostic procedures (n, %)
    - High resolution computed tomography (HRCT)
    - Surgical lung biopsy
    - Chest X-rays
    - 6-minute walk test/pulmonary stress test
    - Spirometry
    - Bronchoalveolar lavage

Treatment on the index date (pharmacological interventions only):

- For each of the following treatments, the number and proportion of patients with and without the treatment on the index date will be reported (days' supply to be considered when exploring treatment use on index)
  - Other treatments (as per ATS/ERS/JRS/ALAT guidelines[19]; n, %)
    - Selective tyrosine kinase inhibitor against platelet derived growth factor (Imatinib)
    - Prednisone
    - Azathioprine
    - N-acetylcysteine
    - Selective endothelin receptor antagonist (ambrisentan)
    - Phosphodiesterase-5 inhibitor (sildenafil)
    - Dual endothelin receptor antagonists (macitentan, bosentan)
  - Corticosteroids (n, %)
    - Inhaled corticosteroids
    - Oral corticosteroids
  - Bronchodilators (n, %)
    - SABA

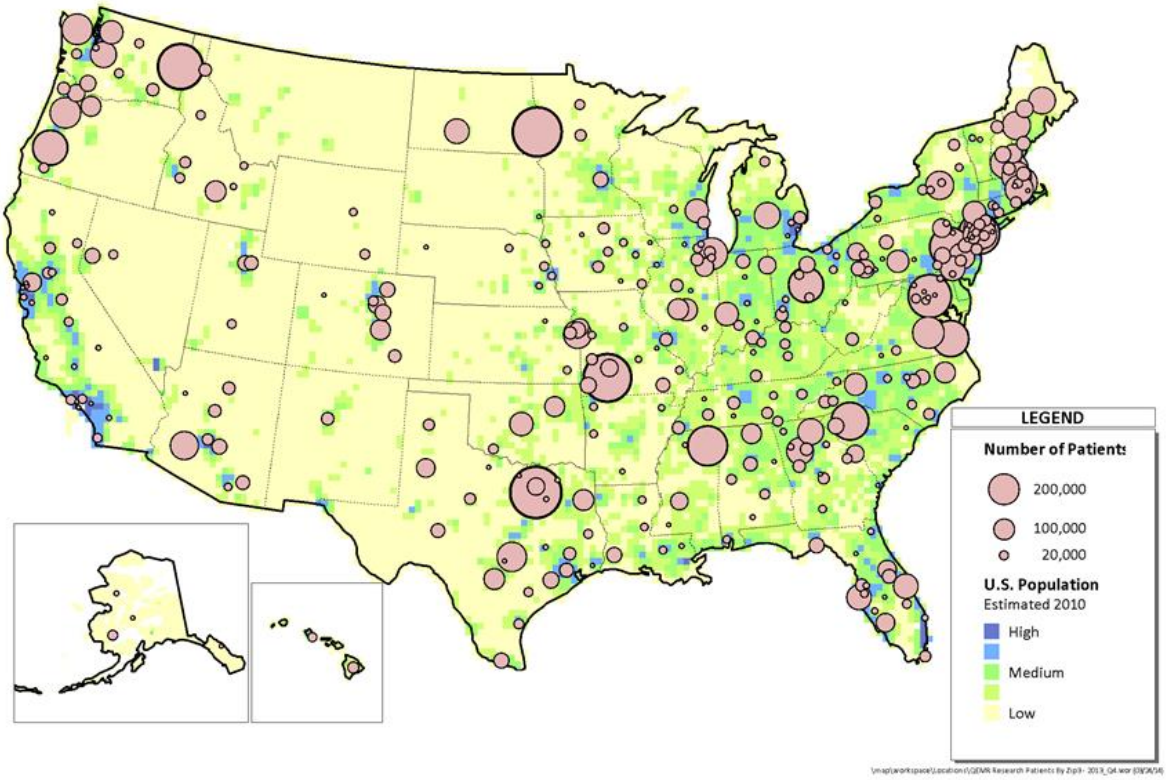
        - LABA
        - Anticholinergics
        - Other beta agonists
    - GERD therapy (n, %)
        - H-2 receptor blockers
        - Proton pump inhibitors
        - Antacids
    - Cardiovascular drugs (n, %)
        - Antianginals
        - Antihypertensives
        - Antiarrhythmics
        - Antiplatelets
        - Anticoagulants
    - Antidiabetes drugs (n, %)
    - Anti-infectives (n, %)
    - Anticonvulsants (n, %)
    - Anti-anxiety drugs (n, %)
    - Antidepressants (n, %)
    - Antipsychotics (n, %)
    - Antihyperlipidemics (n, %)

9.4 DATA SOURCES

GE Centricity EMR database will be used for this study. This is an anonymized Health Insurance Portability and Accountability Act of 1996 (HIPPA) compliant database populated with patient data from ambulatory care records. The EMR database is obtained from a national network of primary care practices (through GE Centricity EMR System) whose providers allow their de-identified patient-level data to be available for research. Clinical data are captured from more than 725 member institutions, more than 43,000 providers and currently captures activity on over 42 million patients from 48 states & the District of Columbia. The EMR had 42 million active patients as of January 2018 and the data continues to grow. Of special interest for this study, there are about 456 Pulmonologist providing their patient data. Additionally, there are about 78 million records from patients covered by Medicare, 69 million from Medicaid, and 58 million records from commercially insured patients.

The size and geographic representation of the data network are illustrated in Figure 2.

Figure 2. Geographic representation of GE Centricity EMR Database



At the individual patient-level, data are processed to provide researchers with demographic information, clinical characteristics (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10 based medical diagnoses, patient complaints), diagnostic tests/results, procedures, insurance information (commercial, Medicare, Medicaid, etc.), and prescription details. Information from specialty healthcare providers (e.g., endocrinologists), and laboratory test orders/results are also available. The data are organized by practice and provide longitudinal medical records for each patient. Comparisons of the EMR patient population to the general population of the United States on demographics (US Census), outpatient visits related to acute and chronic conditions (NCHS-NAMCS), and disease prevalence (NCHS-NHANES) show the EMR is reflective of the US population receiving healthcare in the ambulatory setting.[20,21]

The medical record in the EMR database provides patient level information including the following key analysis variables:

- Age
- Gender
- Race/ethnicity
- Geographic region
- BMI, height, weight
- Systolic BP, Diastolic BP, Pulse

- Procedures performed in outpatient settings (e.g. HRCT, SLB, chest X-rays, spirometry)
- Laboratory values, when recorded (e.g. anticoagulant test, blood counts, kidney and liver function tests)
- Behavioral measures (e.g. smoking status)
- Prescribing physician specialty
- Health insurance details
- Comorbid conditions
- Concomitant medication usage
- Outpatient encounters

9.5 STUDY SIZE

A preliminary feasibility assessment of the most recent EMR data indicates the presence of 2,499 patients newly starting on an IPF treatment (Table 1). 64% of patients are 40 years or above, of which 76% had at least one pulmonary function test. An early feasibility assessment estimated that about 10,000 IPF patients were not treated with antifibrotics.

Considering the orphan nature of IPF and recent FDA approval of these two drugs (within last three years), the EMR database is a good source to extract such a population as it continues to grow. The IPF patients counts are reflective of national estimates (6.8–8.8 per 100,000; <0.01%). The availability of patients should provide sufficient sample to estimate standardized differences in patient characteristics between three cohorts.

Table 1. Preliminary Patient Counts (will vary once study selection criteria are applied, as outlined in Section 9.2)

	Characteristics	Number of patients
1	Evidence of IPF treatment (pirfenidone or nintedanib) between October 1, 2014 to March 30, 2018), first date is index	2,750
2	In #1 with ≥1 EMR before index date	2,508
3	In #2 with no evidence of pirfenidone or nintedanib before index date	2,499
4	In #3 with diagnosis of IPF (ICD-9-CM codes 516.3x, 515, or ICD-10-CM codes J84.112) before index date	2,061
5a	In #4 and with prescription for (mutually exclusive):	1,627
	Pirfenidone only	868
	Nintedanib only	615
	Both Pirfenidone and Nintedanib	144
5b	In #4 and age ≥ 40 years	1,623
5c	In #4 with at least one PFT observations (FEV1, FVC, TLC, Oxygen saturation, OR DCCO) (with non-missing test results) BEFORE index	1,231
6a	In 5c with at least one oxygen saturation value	1,150
6b	In 5c with at least one DCCO value	293

	Characteristics	Number of patients
6c	In 5c with at least one TLC value	217
6d	In 5c with at least one FEV/FVC value	627

9.6 DATA MANAGEMENT

The study will involve use of de-identified EMR data files. Data obtained from the EMR files will be imported into and maintained in a SAS® data analysis file. Tabulation of summary statistics, graphical presentations, and statistical analysis will be performed using SAS® software. The data files are statistically de-identified and don't contain any personal identifiable information. The data are not subject to oversight by the Institutional Review Board (IRB); however, IRB exemption will be obtained. All files will be stored on a secure server and access will be limited to the project team and other authorized personnel.

After applying study inclusion and exclusion criteria, a study database will be created with all of the necessary variables to perform statistical analysis. The aggregated data (in form of counts, %, mean, median, etc.) will be shared with BI at each stage of data programming. The data abstraction will be monitored continuously for quality control purposes, and final results will only be reported after thorough review of programming codes by internal staff members as well as external consultants.

9.7 DATA ANALYSIS

We will ensure internal validity by measuring key study measures and outcomes using a standardized process. All codes and definitions will be reviewed by BI, and any modifications to them can be made prior to delivering the final protocol document.

With respect to external validity, IPF patients will be identified using ICD-9 or ICD-10 diagnosis codes that have been used in previously published studies.[11-13] Pirfenidone and nintedanib, as well as other treatments of interest in this study, will be identified by RxNorm (where available) and a search of drug names (including possible variants of the name). Although there are some potential limitations with generalizability of the study findings, the current study is being conducted using an internal database that contains information on 42 million active patients in the US. Therefore, the findings from our study will have broad generalizability to IPF patients, ensuring appropriate external validity.

9.7.1 Main analysis

For the primary objective, baseline patient characteristics will be described using descriptive analysis, i.e. described as counts and percentages for categorical variables (e.g. gender, race, comorbidities, treatments, diagnostic tests performed) and measures of central tendency (mean, median, SD, and min/max) for continuous variables (e.g., age, lab measures values, BMI). Differences between the cohorts will be assessed using ASD, where an ASD of at least 10% will be considered a meaningful difference.[22] Patients with missing data will be reported as missing and excluded from the comparison for the missing variable.

For continuous variables, the standardized differences will be calculated as

$$d = \frac{(\overline{X}_1 - \overline{X}_2)}{\sqrt{\frac{s_1^2 + s_2^2}{2}}}$$

Where $\overline{X}$ denote sample means in each exposure cohort, and s denotes sample variances.

For categorical variables, the standardized differences will be calculated as

$$d = \frac{(p_1 - p_2)}{\sqrt{\frac{[p_1(1-p_1) + p_2(1-p_2)]}{2}}}$$

Where p denotes proportion of a binary baseline variable in the two exposure cohorts.

The confidence intervals (CIs) for standardized differences will also be calculated as defined below:

$$95\%\ CI = d\ \pm 1.96 \times\ \sigma\ [d]$$

$$where, \sigma\ [d] = \sqrt{\frac{n_1 + n_2}{n_1 \times n_2} + \frac{d^2}{2(n_1 + n_2)}},$$

Where n_i denotes sample sizes of each exposure cohort.

Bivariate statistical significance tests such as Chi-square test for categorical variables and Wilcoxon rank sum test or t-test for continuous variables (depending on distribution of data) will also be performed to compare differences in baseline characteristics between the three cohorts. In addition to standardized differences, p-value in comparing characteristics between the three cohorts will also be reported to help identify "key drivers" associated with treatment selection.

For the second objective, the probabilities of receiving one treatment over another (or nintedanib or pirfenidone vs. untreated) will be tested by propensity scores (PS) and using multivariable logistic regression (possibly with stepwise selection) after controlling for key baseline characteristics (selected based on significance in bivariate analysis or face validity, e.g. age). The similarities and differences between the exposure cohorts will be assessed using balance diagnostics tests (e.g., graphical distribution of overlap between propensity scores of two cohorts (histograms, boxplots), percentage of sample matched, Pearson's correlation coefficient, standardized differences, density estimates, c-statistics, receiver operating characteristic [ROC] curves). Ninety-five percent confidence intervals will be calculated for key parameters. Statistical tests will be two-sided, with α-level of 0.05 for statistical significance.

9.8 QUALITY CONTROL

The study team will be responsible for upholding high levels of quality assurance and control throughout the data analysis and reporting processes. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data. All the modifications to the data will be recorded in an audit trail.

Data validation checks will include checks for missing data and if systematic patterns are observed, adjustments may be made to account for missing data.

Highly qualified personnel from will serve on this project team. will serve as the scientific on the project with serving as the content and strategy advisor, and providing research and delivery support for all project tasks. Each has extensive experience in multiple areas of health outcomes research and epidemiology, with experience working with the numerous BI teams. They will be assisted by clinical experts and research and programming support staff throughout the project.

The project team has experience leading past and ongoing retrospective database studies for BI among IPF patients, and extensive experience conducting research leveraging GE Centricity EMR database.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The major limitation of the study is the lack of generalizability beyond the ambulatory care setting due to the data source. Certain IPF related outcomes such as exacerbation related hospitalizations and ER visits will not be examined due to unavailability in the data source. Additionally, certain IPF related patient characteristics such as lung transplantation may be under reported due to the ambulatory nature of the data. Also specific to the use of an EMR database is the limitation that treatment use will be measured by ≥ 1 prescription; information is not available on if the patient picked up the prescription and adhered to the treatment. This may result in misclassifying patients that did not take their prescriptions as intended or even start the medication, as treated with one of the two study drugs of interest. Also, this study may suffer from limitations common to retrospective database analyses, including possible missing and incorrect data in addition to the fact that data is not collected solely for research purposes. In particular, it is possible that some important covariates could not be included in the PS model due to missing data, leading to a potential bias in representing the choice of treatment in the real world.

9.10 OTHER ASPECTS

None.

9.11 SUBJECTS

The source population will be patients in the GE EMR database, which is representative of the US population receiving healthcare in the ambulatory setting. The eligibility criteria of study subjects are described in detail in Section 9.2.

9.11.1 Cases

Not applicable.

9.11.2 Controls

Not applicable.

9.12 BIAS

To minimize the bias resulting from treatment switching, study selection for new initiators will be used to exclude patients with nintedanib or pirfenidone use prior to index. In addition, an algorithm for IPF identification adapted from claim-based algorithms (see Section 9.2) will be used for the untreated cohort to minimize the bias resulting from misclassifying patients as having IPF or not.[12,13]

10. PROTECTION OF HUMAN SUBJECTS

The database is Health Insurance Portability and Accountability Act (HIPAA) compliant, and all patient data was de-identified before delivery to BI (i.e. existing data). An IRB exemption will be obtained for the study.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Individual case safety reports will not be reported because the GE Centricity EMR database is a secondary database which consists of fully de-identified data. Therefore, it is not possible to assess the causality of individual cases.

Data are anonymized, extracted, analyzed, validated and reported in aggregate. There is no potential that any employee of BI or agent working on behalf of BI will access individual patient data in which the patient may be identified during data compilation, data reporting or data analysis.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Both preliminary and final study results will be delivered to BI. The final study report will include an abstract for presenting the study results at international conferences. The preliminary results will be delivered and presented to BI by February 22, 2019. The final study report will be delivered to BI by June 14, 2019. A manuscript is an optional final deliverable, if of interest to BI.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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13.2 UNPUBLISHED REFERENCES

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

1. *CHANNELING_IPF Diagnostic and Procedure Codes_20181108.xls*
-Contains:
Procedure (including laboratory) codes (Section 9.3.3)
Diagnosis codes for comorbidities (Section 9.3.3)

2. *BI_2477175_Channeling IPF_medication codes 20181107.xls*
Contains:
NDC codes for medications (Section 9.3.3)
HCPCS codes for medications (Section 9.3.3)

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePPChecklistfor StudyProtocols.doc

ANNEX 3. ADDITIONAL INFORMATION

1. Contact information of main parties

Principal Investigator:

O: | M:

Other investigators:

O: | M:

M: