Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c11675456 - 02**
BI Study Number:	1199.252
BI Investigational Product(s):	Not Applicable
Title:	Investigating idiopathic pulmonary fibrosis in Greece (INDULGE IPF)
Brief lay title	INDULGE IPF
Protocol version identifier:	1.10
Date of last version of protocol:	22 February 2018
PASS:	No
EU PAS register number:	Not Applicable
Active substance:	Not Applicable
Medicinal product:	Not Applicable
Product reference:	Not Applicable
Procedure number:	Not Applicable
Marketing authorisation holder(s):	Not Applicable
Joint PASS:	No
Research question and objectives:	The main objective of the study is to gain detailed insights on the characteristics, management and outcomes of patients with IPF as treated under real-world, clinical practice conditions The registry aims to provide information on disease characteristics (disease registry), treatment patterns, long-term effects of IPF and economic aspects
Country(-ies) of study:	Greece
Author:	[redacted]

Marketing authorisation holder(s):	Not Applicable
In case of PASS, add: **MAH contact person:**	Not Applicable
In case of PASS, add: **<EU-QPPV:>**	Not Applicable
In case of PASS, add: **<Signature of EU-QPPV:>**	Not Applicable
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
ALAT	Latin American Thoracic Association
AE	Adverse Event
AESI	Adverse Event of Special interest
ATS	American Thoracic Society
DLCO	Diffusion capacity for carbon monoxide
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
ESC	European Society for Cardiology
ERS	European Respiratory Society
FDA	Food and Drug Administration
FVC	Forced vital capacity
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
[redacted]	[redacted]
HRCT	High resolution chest computer tomography
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
ICMJE	International Committee of Medical Journal Editors
IIP	Idiopathic Interstitial Pneumonia
ILD	Interstitial Lung Disease
IRB	Institutional Review Board
IPF	Idiopathic Pulmonary Fibrosis
JRS	Japanese Respiratory Society
LTx	Lung transplantation
LTOT	Long-term oxygen therapy
NAC	N-acetyl-cysteine
NIS	Non-Interventional Study
NHLBI	National Heart, Lung, and Blood Institute

SAE	Serious Adverse Event
SEAP	Statistical Epidemiological Analysis Plan
SmPC	Summary of Product Characteristics
SEAP	Statistical Epidemiological Analysis Plan
TLC	Total lung capacity
UIP	Usual interstitial pneumonia
ΣΦΕΕ	Hellenic Association of Pharmaceutical Companies

3. RESPONSIBLE PARTIES

Trial Sponsor

[redacted]
Address: [redacted]

Participating Investigators

A contact list of the participating investigators will be stored as a standalone (independent) document and will be available upon request.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Not applicable			
Name of active ingredient: Not applicable			
Protocol date: 29 August 2016	**Study number:** 1199.252	**Version/Revision:** 1.10	**Version/Revision date:** 22 February 2018
Title of study:	Investigating idiopathic pulmonary fibrosis in Greece (INDULGE IPF)		
Rationale and background:	Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs. IPF predominantly presents in older individuals (cases in persons aged less than 50 years are rare), with a preponderance in men and previous or current smokers. Patients present with unexplained chronic exertional dyspnea, and commonly with cough, bibasilar inspiratory crackles, and finger clubbing. IPF is associated with a poor prognosis. Overall, epidemiological data on the incidence and prevalence of IPF are limited, as stated in the consensus statement issued by ATS/ERS/JRS/ALAT. It is unknown if the incidence and prevalence of IPF are influenced by geographic, ethnic, cultural, or racial factors While substantial efforts are being made to investigate the efficacy and safety of new drugs in controlled clinical trials, there is a lack of data on the condition and treatment of patients in clinical practice. In Greece, Karakatsani et al conducted a multicenter research (survey) in 2009, using a one page questionnaire, in order to evaluate the incidence and prevalence of Interstitial Lung Diseases in Greece. Centers covering about 60% of the Greek population have been analyzed. A total of 967 cases of ILDs have been registered. The most frequent disease is sarcoidosis (34.1%), followed in decreasing order by idiopathic pulmonary fibrosis (19.5%). The annual incidence of IPF was estimated to be 0.93 cases per 100,000 whereas prevalence was estimated to be 3.38 cases per 100,000. Since then, the diagnostic criteria, the international guidelines, the standard medical care and the composition of the population have changed. Moreover, a registry can document the introduction of new treatments and complement data that come from the randomized controlled trials.		

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Protocol date: 29 August 2016	**Study number:** 1199.252	**Version/Revision:** 1.10	**Version/Revision date:** 22 February 2018
Research question and objectives:	The main objective of this IPF registry is to gain further knowledge on the characteristics, management, progression and outcomes of patients with IPF as treated under real-world, clinical practice conditions in Greece. More specifically, this registry is going to: • Provide a comprehensive clinical picture for IPF • Track access to health care and cost of caring for IPF patients over time • Examine the implementation of treatment guidelines [2] used on patients diagnosed with IPF, according to the existing diagnosis guidelines [1] Characterization of patients on different treatments		
Study design:	National, multi-center, observational disease registry based on new data from a significant sample size of IPF patients in Greece. Patients will be followed up for 2 years and information will be collected during this time period. This is a non-interventional study and primary data collected during study visits will be used.		
Population:	About 300 patients are going to be included in the study in a consecutive manner, coming from seven (7) Centers in Greece – University Pulmonology Clinics & Reference Centers of Public Hospital Setting – that follow up around 70% - 80% of IPF patients within the Greek territory from April 2017 to April 2019. To be eligible for participation in the study patients must fulfill ALL the inclusion criteria and NONE of the exclusion criteria that are listed below: *Inclusion Criteria* • Newly diagnosed (less than 6 months) or patients previously diagnosed with IPF (more than 6 months prior to baseline visit), based upon the consensus statement jointly issued by ATS/ERS/JRS/ALAT in 2011 (see Annexes 6 and 7 on HRCT and histological criteria in Annex 6). - Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity) - Evaluation of IPF with HRCT or combinations of HRCT and surgical lung biopsy, if available		

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Protocol date: 29August 2016	**Study number:** 1199.252	**Version/Revision:** 1.10	**Version/Revision date:** 22 February 2018
	• Age ≥40 years old at the time of inclusion • Written informed consent for participation in the registry • Patients that can be further followed up by the investigator, during the scheduled study period *Exclusion Criteria* • Expected lung transplantation within the following 6 months Participation in clinical trials		
Variables:	At baseline, a relevant patient history will be recorded including IPF-related events up to 12 months prior to this visit. Further, the current status of IPF patients will be recorded regarding • Basic (Socio-)demographic data • Vital status • Physical and vital signs examination • Cardiopulmonary exercise testing (6-minute walk distance and CPET, if performed) • IPF risk factors • Co-morbidities • Risk of bleeding and thrombosis • Collection of pre-specified outcome data (only for newly diagnosed patients). Please, refer to Annex 3 • Recording of therapeutic regimens. Assessment of the intensity of treatment, frequencies and resource utilization for pharmaco-economic analyses. Methods and procedures used in the diagnosis of IPF and date of diagnosis (including HRCT and SLB) • IPF symptoms • Biomarker results of autoimmune disease • Assessment of function (lung function, cardiopulmonary exercise testing and/or exercise capacity if available) • IPF treatment modalities • Physician's clinical rating of the probable course of IPF(please refer to Table 1 • Clinical events and hospitalizations • Management of IPF and physician contacts		

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	The following will be documented at follow-up : • Clinical course of IPF • Vital status • Physical and vital signs examination • Pulmonary Function Tests (e.g. FVC, DLCO) • Cardiopulmonary exercise testing (6-minute walk distance and CPET, if performed) • Biomarker results of autoimmune disease • Risk of bleeding and thrombosis • Collection of pre-specified outcome data (only for newly diagnosed patients). Please, refer to Annex 3 • Recording of therapeutic regimes. Assessment of the intensity of treatment, frequencies and resource utilization for pharmaco-economic analyses • Clinical evaluation of the potential progression of IPF by the physician (please refer to paragraph 9.3 and Table 1) • Management of IPF and physician contacts		
Data sources:	The study will mainly include the collection of new data recorded in a consecutive manner in an existing web based database (electronic case report form, e CRF).Patients' source data related to their medical history will be derived by the investigators from their medical records and will be documented in the relevant e - CRF section. Data will be collected by the study doctors as they occur according to standard clinical practice. No tests or laboratory procedures that diverge from standard clinical practice are requested.		
Study size:	Approximately 300 patients are going to be included in the study from the participating sites. The number of included patients as well as the duration of the study is not defined by a formal sample size and power calculation, but is mainly based on the availability of eligible IPF patients as well as the patient population in the selected sites. However, a precision table is provided.		
Data analysis:	The objective of this registry is not to confirm or reject any predefined hypotheses. Therefore descriptive statistics will be used for the analysis following standard statistical and epidemiological methods. Continuous variables will be listed as median with interquartile and		

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	other percentages, and as mean value with standard deviation (SD), along with minimum and maximum values. Categorical values will be listed as absolute and relative frequencies. Stratified analyses will be performed among newly diagnosed patients as well as patients that were diagnosed in the past. For outcome analysis the newly diagnosed patients are the decisive one. Due to the limited number of patients and population heterogeneity, no causal relationship conclusion can be derived (no hypothesis testing). Statistical analyses will be performed with IBM SPSS Statistics (Version 19.0).		
Milestones:	Data collection start: April 2017 Data collection end: June 2021 Final report of trial results: June 2022		

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	07 Dec 2017	**4. ABSTRACT**	**Population:** About 300 patients are going to be included in the study in a consecutive manner, coming from seven (7) Centers in Greece – University Pulmonology Clinics & Reference Centers of Public Hospital Setting – that follow up around 70% - 80% of IPF patients within the Greek territory from April 2017 to April 2019.	Increase of the approximate number of patients to be included in the study to 300, in order for the statistical power and validity of the study's results to get strengthened. The increase of the sample size of the present registry has been adopted due to the strong interest of the participating investigators and due to the availability of eligible IPF patients in the selected sites.
2	07 Dec 2017	**4. ABSTRACT**	**Study size:** Approximately 300 patients are going to be included in the study from the participating sites. The number of included patients as well as the duration of the study is not defined by a formal sample size and power calculation, but is mainly based on the availability of eligible IPF patients as well as the patient population in the selected sites. However, a precision table is provided.	Increase of the approximate number of the expected to be included in the study patients to 300, in order for the statistical power and validity of the study's results to get strengthened. The increase of the sample size of the present registry has been adopted due to the strong interest of the participating investigators and due to the availability of eligible IPF patients in the selected sites.

<table>
<tr><th>Number</th><th>Date</th><th>Section of study protocol</th><th>Amendment or update</th><th>Reason</th></tr>
<tr><td>3</td><td>07 Dec 2017</td><td>4. ABSTRACT</td><td>Milestones: Data collection start: April 2017
Data collection end: June 2021
Final report of trial results: June 2022</td><td>Update of the main milestones dates, so that the actual timelines and actual plan to be reflected accurately, based on the visit schedule of the protocol and taking into consideration that the first investigational site was activated on 04 April 2017 and the data collection initiated on 05 Apr 2017.</td></tr>
<tr><td>4</td><td>07 Dec 2017</td><td>6. MILESTONES</td><td><table><tr><th>Milestone</th><th>Planned Date</th></tr><tr><td>IRB/IEC approval</td><td>30 October 2016</td></tr><tr><td>Start of data collection</td><td>05 April 2017</td></tr><tr><td>End of data collection</td><td>05 June 2021</td></tr><tr><td>Final report of study results:</td><td>05 June 2022</td></tr></table></td><td>Update of the main milestones dates, so that the actual timelines and actual plan to be reflected accurately, based on the visit schedule of the protocol and taking into consideration that the first investigational site was activated on 04 April 2017 and the data collection initiated on 05 Apr 2017.</td></tr>
</table>

Number	Date	Section of study protocol	Amendment or update	Reason
5	29 Jan 2018	**9.2 SETTING**	Not applicable	Addition upon request from the reviewing group.
6	07 Dec 2017	**9.3 STUDY SITES**	Physicians managing IPF patients are eligible for participation in the study considering their qualifications, their past participation and experience on similar clinical studies and their capacity on recruiting and monitoring patients in the study. In order to ensure adequate patient numbers per center and high quality of data, expert pulmonary centers will be involved. Seven Centers - University Pulmonology Clinics / Reference Centers of Public Hospital Setting have been selected. Eligible patients will be included in a consecutive manner at each site in order to avoid selection bias. It is possible that the number of Sites will increase in order to achieve representation of the entire Greek territory. A minimum of 15 patients per year should be included per center, to ensure that centers have adequate patient numbers to get accustomed to the study procedures. The number of patients per center is defined in the contractual agreement of each Investigator but may be amended in consultation with the Sponsor, thus allowing the inclusion of more patients. Thus, the study will likely be representative for expert centers in Greece, representing the majority of expert centers in Greece.	Increase of participating centers up to seven (7) compared to the initially defined number of four (4) participating centers. The composition of the participating investigational sites has been modified, as follows: Five (5) University Pulmonology Clinics and two (2) Reference Centers from Public Hospitals

Number	Date	Section of study protocol	Amendment or update	Reason
7	07 Dec 2017	**9.3.3 Study Visits**	The registry is scheduled to run for 4 years in total (2 years recruitment + 2 years follow up) (April 2017 to April 2021). During the follow up period, data will be collected on standard clinical visits which usually are scheduled around: 3-months (+/- 1 month), 6-months (+/- 1 month), 12-months (+/- 2 month), 18-months (+/- 2 month) and 24 months (+/- 2 months), until the end of participation in the study. In case of events, unscheduled visits may be required.	The timeframe of the entire study duration has been updated so that to be in consistency with the actual timelines.
8	29 Jan 2018	**9.4.2 Outcomes**	See sections 9.4.3 & 9.4.4	Addition upon request from the reviewing group.
9	07 Dec 2017	**9.4.5 Covariates** Table 1. List of variables to be documented (if available) at scheduled visits	Table 1. List of variables to be documented (if available) at scheduled visits	Correction on the tabulated schedule of assessments, in Table 1 (List of variables to be documented (if available) at scheduled visits), where the mark X, which corresponds to the variable of (Possible)

<table>
<tr><th>Number</th><th>Date</th><th>Section of study protocol</th><th>Amendment or update</th><th>Reason</th></tr>
<tr><td>9
(continued)</td><td>07 Dec 2017</td><td>9.4.5 Covariates

Table 1. List of variables to be documented (if available) at scheduled visits</td><td>
<table>
<tr><th>Variable (Please refer to Annex 4)</th><th>Assessment</th><th>Follow up**</th></tr>
<tr><td colspan="3">(Possible) IPF risk factors</td></tr>
<tr><td>Cigarette smoking incl. pack years (Categorized
as never/past/current/unknown. For past/current, specify packs/year
and for past, number of years smoking one pack per day);
environmental and occupational exposure; alcohol and substance
abuse; exposure to drugs associated with IPF ; exposure to viral
infection possibly related to IPF; gastro - oesophageal reflux;
genetic factors (family history); others</td><td>x</td><td></td></tr>
</table>
</td><td>IPF risk factors, is deleted from the column of the Follow Up, since that type of data is collected in the context of baseline visit.
The initially printed mark X at the follow up column is characterized as typo error, as it had been printed by mistake.</td></tr>
</table>

Number	Date	Section of study protocol	Amendment or update	Reason
10	07 Dec 2017	**9.6 STUDY SIZE**	This observational study will be analyzed using descriptive statistics following standard statistical and epidemiological methods. Approximately 300 patients are expected to be included in the study in a consecutive manner between April 2017 and April 2019 from the participating sites according to the feasibility procedure of the sites.	Increase of the approximate number of the expected to be included in the study patients to 300, in order for the statistical power and validity of the study's results to get strengthened. The increase of the sample size of the present registry has been adopted due to the strong interest of the participating investigators and due to the availability of eligible IPF patients in the selected sites. In parallel, the timeframe of the enrolment period has been updated so that to be in line with the actual timelines.
11	16 Feb 2018	**9.6 STUDY SIZE**	Table 2 describes the expected precision for the description of a proportion, according to different sample sizes. Note that within Table 2 the first interval relates to an asymptotic 95% confidence interval and the second interval relates to an exact 95% confidence interval (i.e. The Clopper-Pearson interval).	Due to the revision of Table 2 which presents the confidence intervals, based on the calculations from two different statistical methods. The revised Table 2 incorporates the respective calculations in relation to the new sample size of 300 patients.

<table>
<tr><th>Number</th><th>Date</th><th>Section of study protocol</th><th>Amendment or update</th><th>Reason</th></tr>
<tr><td>12</td><td>16 Feb 2018</td><td>9.6 STUDY SIZE

Table 2. Precision of estimates for binary parameters</td><td>Table 2. Precision of estimates for binary parameters
<table>
<tr><th rowspan="2">(Sub) group size</th><th colspan="5">Proportion</th></tr>
<tr><th>50%</th><th>40%</th><th>30%</th><th>20%</th><th>10%</th></tr>
<tr><td>50</td><td>(36.14%, 63.86%)</td><td>(26.42%, 53.58%)</td><td>(17.30%, 42.70%)</td><td>(8.91%, 31.09%)</td><td>(1.68%, 18.32%)</td></tr>
<tr><td></td><td>(35.53%, 64.47%)</td><td>(26.41%, 54.82%)</td><td>(17.86%, 44.61%)</td><td>(10.03%, 33.72%)</td><td>(3.33%, 21.81%)</td></tr>
<tr><td>100</td><td>(40.20%, 59.80%)</td><td>(30.40%, 49.60%)</td><td>(21.02%, 38.98%)</td><td>(12.16%, 27.84%)</td><td>(4.12%, 15.88%)</td></tr>
<tr><td></td><td>(39.83%, 60.17%)</td><td>(30.33%, 50.28%)</td><td>(21.24%, 39.98%)</td><td>(12.67%, 29.18%)</td><td>(4.90%, 17.62%)</td></tr>
<tr><td>200</td><td>(43.07%, 56.93%)</td><td>(33.21%, 46.79%)</td><td>(23.65%, 36.35%)</td><td>(14.46%, 25.54%)</td><td>(5.84%, 14.16%)</td></tr>
<tr><td></td><td>(42.87%, 57.13%)</td><td>(33.15%, 47.15%)</td><td>(23.74%, 36.86%)</td><td>(14.69%, 26.22%)</td><td>(6.22%, 15.02%)</td></tr>
<tr><td>300</td><td>(44.34%, 55.66%)</td><td>(34.46%, 45.54%)</td><td>(24.81%, 35.19%)</td><td>(15.47%, 24.53%)</td><td>(6.61%, 13.39%)</td></tr>
<tr><td></td><td>(44.20%, 55.80%)</td><td>(34.41%, 45.79%)</td><td>(24.87%, 35.53%)</td><td>(15.62%, 24.98%)</td><td>(6.85%, 13.97%)</td></tr>
</table></td><td>Inclusion of the newly calculated confidence intervals, based on the new sample size (300 pts) into a revised Table 2. The revised Table 2 presents more accurately the 95% confidence intervals based on the calculations from two different statistical methods, comparing to the original Table 2.</td></tr>
</table>

Number	Date	Section of study protocol	Amendment or update	Reason
13	07 Dec 2017	**9.10 LIMITATIONS OF THE RESEARCH METHODS**	The study is going to provide evidence regarding the situation in the IPF reference centers which are University Pulmonology Clinics and Pulmonology Clinics at Hospitals of Public Setting that follow up about 70%-80% of IPF patients in Greece.	Increase of participating centers up to seven (7) compared to the initially defined number of four (4) participating centers. The composition of the participating investigational sites has been modified, as follows: Five (5) University Pulmonology Clinics and two (2) Reference Centers from Public Hospitals

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	30 October 2016
Start of data collection	05 April 2017
End of data collection	05 June 2021
Final report of study results:	05 June 2022

7. RATIONALE AND BACKGROUND

7.1 DEFINITION

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs[1]. It is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis. As stated in an international consensus statement jointly issued by ATS/ERS, JRS and ALAT, IPF is a distinct clinical entity associated with the histologic and/or radiologic appearance of usual interstitial pneumonia (UIP) [1]. The definition of IPF requires the exclusion of other forms of interstitial pneumonia including other idiopathic interstitial pneumonias (IIP) and interstitial lung disease (ILD) associated with environmental exposure, medication, or systemic disease [1].

IPF predominantly presents in older individuals (cases in persons aged less than 50 years are rare), with a preponderance in men and previous or current smokers. Patients present with unexplained chronic exertional dyspnea, and commonly with cough, bibasilar inspiratory crackles, and finger clubbing.

7.2 INCIDENCE AND PREVALENCE

Overall, epidemiological data on the incidence and prevalence of IPF are limited, as stated in the consensus statement issued by ATS/ERS/JRS/ALAT [1].

In a population-based study from New Mexico, the incidence of IPF was estimated at 10.7 cases per 100,000 per year for men and 7.4 cases per 100,000 per year for women [1]. In the UK, an overall incidence rate of only 4.6 per 100,000 person-years was reported, however, with an estimated increase by 11% annually between 1991 and 2003 (not attributed to aging of the population or increased ascertainment of milder cases) [4]. In the USA, based on a large database of healthcare claims in a health plan, the incidence of IPF was estimated between 6.8 and 16.3 per 100,000 persons [5].

Prevalence estimates for IPF, as assessed in England, Japan, New Mexico, Norway, Italy and Greece , have varied widely from 1,82 to 35,51 cases per 100,000 in the general population [2, 6-9, 26]. The wide range in these numbers is likely explained by the previous lack of uniform definition used in identifying cases of IPF, as well as by differences in study designs and populations [1]. In the USA, a recent analysis based on healthcare claims yielded a prevalence estimate between 4.0 - 42.7 per 100,000 persons depending on the case definition used [5]. Another study from the US, estimated a prevalence of 58.7 per 100,000 (95% CI 56.3-61.2) for IPF, after correction of the estimate for its PPV after chart review [27]. It is unknown if the incidence and prevalence of IPF are influenced by geographic, ethnic, cultural, or racial factors [1]. In Italy, a relevant study from N. Agabiti,M. A. Porretta, L Bauleo, A. Coppola, et al, conducted at Lazio region, concluded that IPF incidence and prevalence in this large central-southern Italian region are strikingly similar to those derived from the hospital and general medicine databases of northern Europe and the United States. At the same time, this study stated that IPF incidence is more likely driven by industrialization, urbanization and western lifestyles than the ethnic variables characterizing different European regions[25]. In 2016, another study conducted in Lombardy, the most populous region of Italy, estimated the annual incidence and prevalence at 7.5 and 25.6 per

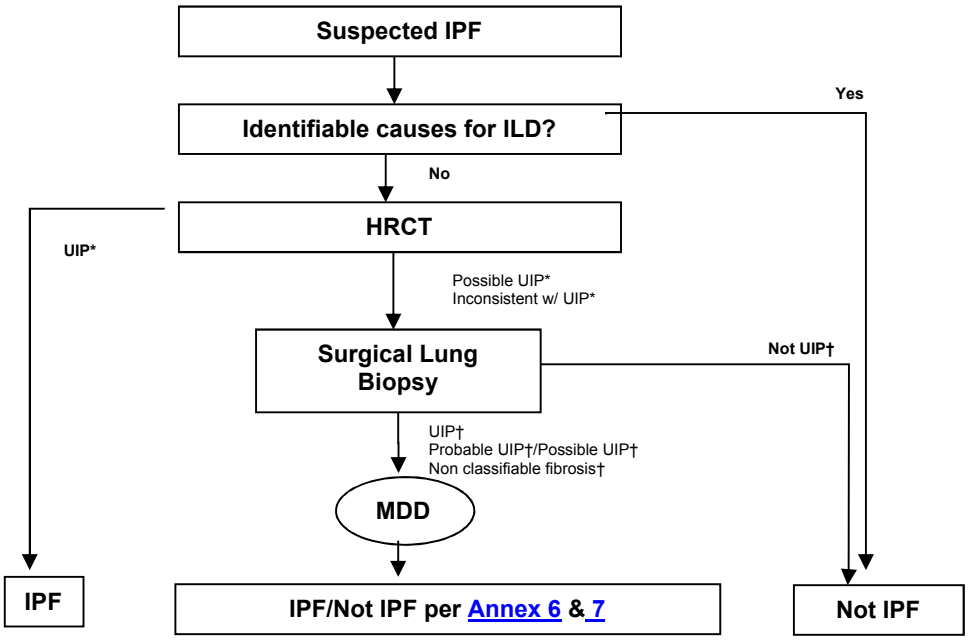
100,000 person-years, respectively. This same study indicated that prevalence of IPF increased across the years while incidence remained stable, concluding that survival with IPF has improved. However, Italian trends in incidence and prevalence of IPF are still unknown [26].

7.3 DIAGNOSIS

According to the consensus statement jointly issued by ATS/ERS/JRS/ALAT in 2011, the diagnosis of IPF requires the following [1]:

- Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
- The presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy
- Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy

Figure 1. Diagnostic algorithm according to ATS/ESC/ERS/JRS/ALAT guidelines [1]



7.4 NATURAL COURSE

Data on the natural course of IPF are from retrospective and a few prospective studies, including the placebo arms of clinical trials (limited to short observation periods and by in-/exclusion criteria). The previously reported median survival time of 2-3 years from the time of diagnosis could be an underestimate, at least when accounting for patients with preserved lung function. Notably, the natural course is unpredictable for a given patient at the time of diagnosis, while the majority of patients experience steady worsening (slow progression), other remain stable, or have rapid progression of disease [10-11]. Acute respiratory worsening either due to secondary complications (e.g. pneumonia, pulmonary embolism, pneumothorax or cardiac failure) or due to unknown reasons (in this case the term acute exacerbation is used) are suggested to occur in about 5-10% annually [1]. A recent retrospective review of 461 patients with IPF has found that the 1- and 3-year incidences of acute exacerbations were 14.2% and 20.7%, respectively [12].

7.5 THERAPY

The ATS/ESR/JRS/ALAT guideline finalized end of 2010 and issued in 2011 stated: "The committee did not find sufficient evidence to support the use of any specific pharmacologic therapy for patients with IPF." [1]

A number of drugs are used for the treatment of IPF, including steroids, azathioprine and N-acetylcysteine (and sometimes the latter three in combination). However, recently the NHLBI (part of the National Institutes of Health) has stopped the triple- drug therapy arm consisting of prednisone, azathioprine, and N-acetylcysteine (NAC) of the US PANTHER trial due to safety concerns. [13]

The only drug that until recently had received regulatory approval for the treatment of mild or moderate IPF in Europe and Japan was pirfenidone, a pyridone compound with pleiotropic, anti-inflammatory, antifibrotic, and antioxidant properties, with antagonism of TGF-b1 effects [14]. On October 2014, FDA approved simultaneously pirfenidone and nintedanib, a tyrosine kinase inhibitor that was researched and developed by Boehringer Ingelheim [15] for IPF treatment. Moreover, on January 15, 2015 EMA approved the use of nintedanib on all IPF stages. According to the updated Guidelines for IPF treatment, released on July of 2015, conditional recommendations have been made for treatment with novel agents such as pirfenidone and nintedanib, as well as antiacid treatment. The treatment of IPF patients should be individualized, according to the patient and the physician should calculate the benefit of using one intervention instead of another [2]. New drugs for IPF treatment will also be documented in this registry.

As for supportive pharmacological and non-pharmacological therapy, the evidence is limited, too. This includes anticoagulants, long-term use of oxygen, mechanical ventilation and lung transplantation [1].

7.6 ECONOMIC ASPECTS

IPF is of high interest for the health-care system as well as for payers when considering costs. However, data on economic issues are limited, while needed for assessing cost-effectiveness of interventions [16-17].

The current IPF Registry will be suitable for various cost analyses. All pharmaco- and health economic parameters will be derived from either one or both of the following ways and in most cases subsequently priced:

- Assessment of the direct health resources use
- Indirect health assessment with adjustment of recorded clinical outcomes.

7.7 RATIONALE FOR THE PRESENT REGISTRY

Long-term data on the natural course of IPF are missing. Further, there is lack of information on detailed patient characteristics. While in IPF substantial efforts are being made to investigate the efficacy and safety of new drugs in controlled clinical trials, there is a lack of data on the situation and treatment of patients in everyday clinical practice. In a call for action on an IPF registry by Wilson in 2008, it was noted that improved survival from this disease is dependent on better understanding of the epidemiology of the disease, its diagnostic spectrum and an analysis of outcomes from emerging therapies at a significant level. [17] In Greece, Karakatsani et al, conducted a multicenter research (survey) in 2009, using a one page questionnaire, in order to evaluate the incidence and prevalence of Interstitial Lung Diseases in Greece. The annual incidence of IPF was estimated to be 0.93 cases per 100,000 whereas prevalence was estimated to be 3.38 cases per 100,000. Since then, the diagnostic criteria, the international guidelines [1] the standard medical care and the composition of the population have changed, whereas more studies have been conducted regarding the incidence and prevalence of IPF (please refer to Section 7.2).

A registry can document the introduction of new treatments and complement data from the controlled randomized trials. The present clinical IPF registry will record standard epidemiological parameters by using a web-based electronic case report form. No additional biobank specimen will be collected (only already existing data will be used from examinations that have been performed according to the routine clinical practice of the physicians). IPF diagnosis will be based upon criteria, defined according to the consensus statement jointly issued by ATS/ERS/JRS/ALAT for the collection of standard practice data, and as it is also described in the inclusion criteria section. Moreover, in the present IPF registry, drug utilization and treatment patterns under clinical practice conditions will be documented in detail. Furthermore, health economic aspects will be investigated.

8. RESEARCH QUESTION AND OBJECTIVES

The overall objective of the present IPF Registry is to gain further insight on the characteristics, management, disease progression and the outcomes of patients with IPF, as diagnosed and treated under real-world, clinical practice conditions in Greece.

More specifically, this registry will be used to:

- Provide a comprehensive clinical picture of IPF
- Track access to health care and cost of caring for IPF patients over time
- Examine the implementation of treatment guidelines [2], used on patients diagnosed with IPF, according to the existing diagnosis guidelines [1]
- Characterization of patients on different treatments

Furthermore, this project aims to provide information regarding survival and mortality causes, IPF exacerbations as well as IPF patient co-morbidities including myocardial infarction, CNS infarction, other arterial thromboembolic events, deep vein thrombosis, hemorrhage, gastrointestinal perforation and pulmonary hypertension (please refer to Annex 3). In addition, data regarding IPF patient hospitalization will be collected and evaluated with regards to potential respiratory causes, and there will be documentation of treatment patterns and economic aspects. Patients will be followed up for 2 years and information regarding IPF treatment changes since the last visit will be collected.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This IPF registry allows for structured, non-interventional collection of data. A similar protocol was prepared by the [redacted] of the [redacted] ([redacted]). This Protocol is based on the main idea of the protocol created by the [redacted] It is a national, multi-center, observational disease and outcomes registry based on new data from a significant sample size of Greek IPF patients. Participating physicians (experts in IPF) will not be subject to any instructions with regard to the diagnosis and therapy of their patients. All examinations performed depend on the discretion and clinical routine of the physician.

The Sponsor of the Study will be [redacted] and will own the data and have access to the data. Members of the National Scientific Committee (see title page) will oversee and give scientific advice for the study.

An external Vendor (CRO) will provide the electronic database; the web based eCRF and will perform the statistical analyses and produce the relevant reports according to the Statistical Epidemiological Analysis Plan.

This IPF Registry is not a clinical trial (interventional study) according to the Ministerial Decision No 12/2003 of the Greek Legislation for Clinical Studies, but a non- interventional observation study.

9.2 SETTING

Not applicable

9.3 STUDY SITES

Physicians managing IPF patients are eligible for participation in the study considering their qualifications, their past participation and experience on similar clinical studies and their capacity on recruiting and monitoring patients in the study. In order to ensure adequate patient numbers per center and high quality of data, expert pulmonary centers will be involved. Seven Centers - University Pulmonology Clinics / Reference Centers of Public Hospital Setting have been selected. Eligible patients will be included in a consecutive manner at each site in order to avoid selection bias. It is possible that the number of Sites will increase in order to achieve representation of the entire Greek territory. A minimum of 15 patients per year should be included per center, to ensure that centers have adequate patient numbers to get accustomed to the study procedures. The number of patients per center is defined in the contractual agreement of each Investigator but may be amended in consultation with the Sponsor, thus allowing the inclusion of more patients. Thus, the study will likely be

representative for expert centers in Greece, representing the majority of expert centers in Greece.

9.3.1 Study Population

Eligible for participation in the study patients must fulfill **ALL** the inclusion criteria and **NONE** of the exclusion criteria that are listed below and must be consecutively enrolled:

- Newly diagnosed (less than 6 months) or patients previously diagnosed with IPF (more than 6 months from baseline visit), based upon the consensus statement jointly issued by ATS/ERS/JRS/ALAT in 2011 (see Annex 6 and Annex 7 for HRCT and histological criteria in Annex 6)
  - Exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity)
  - Assessment of IPF based on HRCT or combinations of HRCT and surgical lung biopsy, if available
- Age ≥40 years old at the time of inclusion
- Written informed consent for participation in the registry
- Patients that can be followed up further, during the scheduled study period

None of the following Exclusion Criteria should be fulfilled:

- Expected lung transplantation within the following 6 months
- Participation in clinical trials

Patients will be included in a consecutive manner at each site in order to avoid selection bias. It should be avoided to establish the registries at sites where already other registries are ongoing (if a patient participates in another registry/non - interventional study this needs to be documented and patients need to be analyzed separately).

A subject screening log should be kept at the site, recording basic information (e.g. initials, gender, date of birth, reason for not enrolling the patient etc.) on all patients who were invited to participate in the study, with the information on the eligibility (or reasons for non-eligibility) and date of signed informed consent. In the case of refusal, reasons for refusal should be given. In addition, a log of all patients included into the study (i.e. having given informed consent) will be maintained in the study file at the study site.

9.3.2 Withdrawal Criteria

The patients reserve the right to withdraw consent at any time during the study, without the need for justification and without any impact on their future treatment and care.

Withdrawal of consent means that the patient does not wish or cannot continue to participate in the study any more.

The reasons for withdrawal may include the following:

- Patient or legally accepted representative withdraws informed consent for participation in the study.
- Inclusion or possible participation in any clinical trial, any time within the follow up period of the study, in which the patient has been exposed or is going to be exposed to an investigational product (pharmaceutical product or medical device) or intervention.
- The patient was erroneously included in the registry
- Decision of the investigator/physician
- Important deviation/divergence from the protocol.

The Clinical Monitor at BI or BI's designees must be immediately notified if a patient is discontinued prematurely for any of the instances reasons cited above.

Patients that withdraw from the study should be asked about the reason(s) for withdrawal and the occurrence of adverse events, and should be examined and evaluated by the investigator according to the procedures that are defined in the Final Visit (unless reason for discontinuation is erroneous enrolment of the patient into the study at baseline and unless patient has actively withdrawn consent for any kind of future contacts).

If the patient specifically withdraws consent for future contact about the collection of further information, there will be no such contact whatsoever. However, it is possible to collect information regarding their survival status, if they are publicly available.

The investigators also reserve the right to remove a patient from the study, if according to their clinical judgment this is the necessary for the patient's welfare.

If a patient is removed or withdrawn from the study for any reason, the date, vital status and reason must be documented in the relevant section of the electronic Case Report Form (eCRF).

9.3.3 Study Visits

The registry is scheduled to run for 4 years in total (2 years recruitment + 2 years follow up) (April 2017 to April 2021).

During the follow up period, data will be collected on standard clinical visits which usually are scheduled around: 3-months (+/- 1 month), 6-months (+/- 1 month), 12-months (+/- 2 month), 18-months (+/- 2 month) and 24 months (+/- 2 months), until the end of participation in the study. In case of events, unscheduled visits may be required.

9.3.4 Study Discontinuation

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site
2. Violation of Good Clinical Practice (GCP) (as applicable), the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination (except in case of the third reason).

9.4 VARIABLES

At baseline, a relevant patient history will be recorded including IPF-related events up to 12 months prior to this visit. The variables to be recorded are listed below as well as in Annex 4:

- Basic (socio-)demographic data including age, gender and race
- Vital Status
- Physical and vital signs examination
- Cardiopulmonary exercise testing (6-minute walk distance and CPET, if performed)
- IPF risk factors (e.g cigarette smoking including pack years, alcohol and substance abuse, environmental and occupational exposure, exposure to drugs associated with IPF , exposure to viral infection possibly related to IPF, gastro-esophageal reflux, genetic factors - family history)
- Co-morbidities.
- Risk of bleeding and thrombosis
- Collection of pre-specified outcome data, only for newly diagnosed patients (such as acute respiratory worsening, exacerbations, hospitalization due to any cause and due to IPF). Please, refer to Annex 3
- Recording of therapeutic regimens. Assessment of the intensity of treatment, frequencies and resource utilization for pharmaco-economic analyses.
- Methods and procedures used in the diagnosis of IPF and date of diagnosis (HRCT: UIP pattern, possible, inconsistent UIP pattern and not available and SLB: UIP pattern, probable, possible or inconsistent UIP pattern)
- IPF symptoms: Dyspnea, cough, weight loss, fatigue, dizziness, chest pain, anxiety, clubbing, bibasilar crackles
- Autoimmune Biomarker results (No additional specimen will be collected. Only already existing data will be used from exams that have been performed according to the routine clinical practice of the physicians),
- Assessment of function (including lung function, cardiopulmonary exercise testing and/or exercise capacity if available, laboratory values)
- IPF treatment modalities (detailed information on prescribed drugs and dose; previous treatment; start and end dates of previous treatments; non-pharmacological treatment; listing and score for lung transplantation). For the treatments that detailed information will be requested, please refer to Annex 4

- Physician's clinical rating of the probable course of IPF (stable, slow or rapid progression)
- Clinical events and hospitalizations especially due to: (acute) respiratory worsening, including pneumonia, exacerbations of IPF, occurrence of pulmonary or cardiovascular complications, pulmonary rehabilitation, pulmonary embolism, pneumothorax, or cardiac failure
- Management of IPF and physician contacts

During follow up visits (prospectively until up to 2 years at least from the inclusion) 3-months (+/- 1 month), 6-months (+/- 1 month), 12-months (+/- 2 month), 18-months (+/- 2 month) and 24 months (+/- 2 months), documentation of events (or last follow up visit) will be carried out. The collection of data will be performed during standard clinical practice visits (i.e. visits should not be performed via telephone contact). In a special event where the physical presence of the patient is not possible, e.g. in case of temporary inability of the patient to visit the expert center, this visit could be performed through telephone contact and this should be recorded in patient's history. Every effort should be made, however, to ensure that the next visit will be performed as planned by the patient in person. If this is not possible the patient will be censored for the rest of the study. Patient will be followed up until death, lung transplantation, consent withdrawal or end of study, whichever comes first and will be censored if one of the events occurs. The following data will be documented:

- Clinical course of IPF (e.g. regarding symptoms, lung functionality, exercise ability, if available)
- Vital status
- Physical and vital signs examination
- Cardiopulmonary exercise testing (6-minute walk distance and CPET, if performed)
- Autoimmune Biomarker results (No additional specimen will be collected. Only already existing data will be used from exams that have been performed according to the routine clinical practice of the physicians)
- Risk of bleeding and thrombosis
- Outcomes of interest (such as acute respiratory worsening, exacerbations, hospitalization due to any cause and due to IPF). Please, refer to Annex 3
- Recording of therapeutic algorithms (change/complement/interrupt treatment) and non-pharmacological treatment (e.g. start of LTOT, new listing for lung transplantation)
- Physician's clinical rating of the probable course of IPF (stable, slow or rapid

progression)

- Assessment of treatment intensity, frequencies and resource use for pharmacoeconomic analyses for the treatments described under 11.3
- Management of IPF and physician contacts

9.4.1 Exposures

Not Applicable

9.4.2 Outcomes

See sections 9.4.3 & 9.4.4

9.4.3 Primary Outcomes

The main objective of this IPF registry is to gain further knowledge on the characteristics, management, progression and outcomes of patients with IPF as treated under real-world, clinical practice conditions in Greece.

More specifically, this registry is going to:
- Provide a comprehensive clinical picture for IPF
- Track access to health care and cost of caring for IPF patients over time
- Examine the implementation of treatment guidelines [2], used on patients diagnosed with IPF, according to the existing diagnosis guidelines [1]
- Characterization of patients on different treatments

For more detailed information, please refer to Annex 3.

9.4.4 Secondary Outcomes

This registry documents management and treatment of IPF-patients in real-world clinical practice. One objective of this registry is to document drugs used for IPF.

The following drugs will be documented in detail in terms of drug name, dosage, start and stop dates, including combinations of the mentioned drugs:

- Steroids
- Immunomodulators (azathioprine, cyclophosphamide, cyclosporine A, mycophenolate mofetil etc)
- N-Acetylcysteine
- Pirfenidone
- Nintedanib
- Anticoagulants

- Vit-K antagonist
- Heparin
- Antiplatlet therapy (if yes it will be specified if high dose antiplatlet therapy)
- Aspirin (if yes it will be specified if used as antiplatelet)
- GERD medication
- PDE-5 inhibitor (sildenafil, tadalafil)
- Endothelin receptor antagonist (bosentan, ambrisentan, macitentan)
- Long term oxygen therapy
- Listed for lung transplantation
- NSAIDs, other than aspirin
- Hormone replacement therapy
- Hormonal contraceptives
- Anti-VEGF drugs
- NOAC
- Other (specify)

9.4.5 Covariates

Due to the non - interventional nature and design of the observational study, this registry does not require diagnostic/therapeutic procedures or strict timeline visit schedule. Patients will receive treatment according to standard clinical practice with regards to visit frequencies, type of performed assessments and according to local prescription requirements.

Following identification of a potential patient, the investigator will follow the below listed procedures:

1. Review of individual patient's medical history, to confirm that the inclusion/exclusion criteria are met.
2. Explanation of the study objectives to the patient and receipt of signed and dated informed consent, after providing the patient with sufficient time to read carefully and understand the information sheet.
3. Data collection from the medical records of eligible for enrollment patients, as required by eCRF, and eCRF completion.

Please refer to Section 11.2 for details regarding Adverse Event and Serious Adverse Event Collection and Reporting.

A tabulated schedule of assessments that provide information regarding the recommended timeline of data collection and represents the standard clinical care of IPF treated patients is listed below in Table 1. The exact definitions of the variables can be found in Appendixes 2-5.

Table 1. List of variables to be documented (if available) at scheduled visits

Variable (Please refer to Annex 4)	***Assessment***	***Follow up*****
Eligibility criteria	x	
Baseline information (assessment)		
(Socio-)demographic variables: age, gender, race, height, index employment status, insurance status	x	
Weight, blood pressure, heart rate	x	x
(Possible) IPF risk factors		
Cigarette smoking incl. pack years (Categorized as never/past/current/unknown. For past/current, specify packs/year and for past, number of years smoking one pack per day); environmental and occupational exposure; alcohol and substance abuse; exposure to drugs associated with IPF ; exposure to viral infection possibly related to IPF; gastro-oesophageal reflux; genetic factors (family history); others	x	
Co-morbidities *(Please refer to Annex 5)*	x	x
IPF Baseline information (assessment) on IPF		
First symptoms; date of first diagnosis, dates and results of HRCT, surgical lung biopsy, bronchoalveolar lavage.	x	
Symptoms		
9.4.5.1 Dyspnea, cough fatigue, dizziness, chest pain, anxiety [20]	x	x
Functional assessment		
Lung function test (VCin, FVC, FEV1, TLC; DLCO; pO2, pCO2) [21] 6-minute walk distance Cardiopulmonary exercise testing (CPET;)	x	x
Serologic evaluation– Autoimmune Biomarkers (laboratory values)		
Rheumatoid factor, anti-cyclic citrullinated peptide, and anti-nuclear antibody titer and pattern* Others e.g. SCL-70, SS-A, SS-B	x	x

BNP/NT-pro BNP Hb, AST, ALT, total bilirubin		
Pharmacological treatment(start date, stop date and daily dose)		
Past/discontinued: drugs (e.g. steroids yes/no/unknown). Detailed list of drugs in Annex 4	x	x
Current: drugs by class and/or name	x	x
Participation in IPF trial	x	x
Non-pharmacological treatment	x	x
Long-Term-Oxygen-Therapy (liquid and/or concentrate)	x	x
Lung transplantation score and assessment if the patient is currently listed for participation in lung transplantation	x	x
Physician assessment		
Physician's clinical rating of the probable course of IPF (stable, slow or rapid progression), based on available FVC results, DLCO results, physical examination, hospitalizations/events between the visits	x***	x
Management of IPF and physician contacts		
Number of physician visits (own office, other physicians)	x***	x
Number and type of IPF related procedures	x***	x
Outcomes of Interest (please refer to Annex 3)	x*** (except for mortality, hospitalization, please see below)	x
Clinical events and hospitalizations		
specifically due to: (acute) worsening of respiratory function including pneumonia; IPF-exacerbations; manifest pulmonary or cardiovascular complications; pulmonary rehabilitation; pulmonary embolism; pneumothorax; cardiac failure (please refer to Annex 3 for detailed description of the outcomes of interest).	x***	x
Number of days in hospital or in rehabilitation; work days lost due to IPF	x***	x
Physical examination and vital signs	x	x
Risk of bleeding and thrombosis	x	x

Survival status (vital status)(please refer to Annex 3)		x

For abbreviations, please refer to glossary.

* As recommended in the ATS/ERS guidelines for distinguishing connective tissue disease from IPF

**3-months (+/- 1 month), 6-months (+/- 1 month), 12-months (+/- 2 month), 18-months (+/- 2 month) and 24 months (+/- 2 months)
*** *the past 12 months*

9.5 DATA SOURCES

The study will mainly include the recording of new data through a web based system for data collection. Data will be collected by the study doctors as they occur according to standard clinical practice in the approximate visiting schedule indicated above.

Source (primary) patient data related to their medical and IPF history will be collected by the investigators from the patient's medical files/records and will be documented in the relevant eCRF section.

Data regarding treatment modifications, concomitant treatments, study related routine clinical assessments, adverse events (ADRs) and survival status will also be collected. If a patient withdraws early from the study, they will be contacted via telephone at the end of the Study in order to evaluate their survival status. Another follow-up assessment should be performed if possible (unless reason for discontinuation is erroneous enrolment of the patient into the study at baseline), and data should be entered on the eCRF of the next planned visit unless the patient has actively withdrawn consent for any kind of future contacts.

9.6 STUDY SIZE

This observational study will be analyzed using descriptive statistics following standard statistical and epidemiological methods. Approximately 300 patients are expected to be included in the study in a consecutive manner between April 2017 and April 2019 from the participating sites according to the feasibility procedure of the sites.

The number of included patients as well as the duration of the study is not defined by a formal sample size and power calculation, but is based mainly on the availability of eligible IPF patients as well as patient population in the selected sites.

Table 2 describes the expected precision for the description of a proportion, according to different sample sizes. Note that within Table 2 the first interval relates to an asymptotic 95% confidence interval and the second interval relates to an exact 95% confidence interval (i.e. The Clopper-Pearson interval).

Table 2. Precision of estimates for binary parameters

(Sub) group size	Proportion				
	50%	40%	30%	20%	10%
50	(36.14%, 63.86%)	(26.42%, 53.58%)	(17.30%, 42.70%)	(8.91%, 31.09%)	(1.68%, 18.32%)
	(35.53%, 64.47%)	(26.41%, 54.82%)	(17.86%, 44.61%)	(10.03%, 33.72%)	(3.33%, 21.81%)
100	(40.20%, 59.80%)	(30.40%, 49.60%)	(21.02%, 38.98%)	(12.16%, 27.84%)	(4.12%, 15.88%)
	(39.83%, 60.17%)	(30.33%, 50.28%)	(21.24%, 39.98%)	(12.67%, 29.18%)	(4.90%, 17.62%)
200	(43.07%, 56.93%)	(33.21%, 46.79%)	(23.65%, 36.35%)	(14.46%, 25.54%)	(5.84%, 14.16%)
	(42.87%, 57.13%)	(33.15%, 47.15%)	(23.74%, 36.86%)	(14.69%, 26.22%)	(6.22%, 15.02%)
300	(44.34%, 55.66%)	(34.46%, 45.54%)	(24.81%, 35.19%)	(15.47%, 24.53%)	(6.61%, 13.39%)
	(44.20%, 55.80%)	(34.41%, 45.79%)	(24.87%, 35.53%)	(15.62%, 24.98%)	(6.85%, 13.97%)

For continuous endpoints, precision of estimates will depend on parameter specific assumptions on mean and standard deviation. A generic display as given for binary endpoints is therefore less appropriate.

9.7 DATA MANAGEMENT

The registry will include the collection of new data that will be recorded in an existing web based database in a consecutive manner (electronic case report form, eCRF) as well as transferring already existing data to the system from medical charts. The patients will be identified by subject identification number, site number, and study identification number.

Investigators will enter the data of their patients directly into an internet-based electronic case record form. At data entry, plausibility checks (e.g., range checks, conditional checks, etc.) will be performed. Data will be entered in the eCRF system by the study personnel at the Investigator's site, according to the Investigator Instructions Manual. Data entered in the eCRF system will be automatically saved to a central database and changes tracked to provide an audit trail. When data have been entered, reviewed and edited, the Investigator shall sign the e-CRF electronically as per the agreed project process and data will be locked to prevent further editing.

Query management will be performed through built-in query management functionality that will be incorporated into the eCRF.

Prior to the onset of data management activities, a detailed data management plan (DMP) will be issued describing the procedure to be followed for processing all collected study data in order to ensure they are valid, complete and accurate for statistical analysis. In addition, aiming at ensuring the expected quality of data, a thorough data cleaning session will be applied. When all data have been properly validated and the quality control procedure has been completed, a declaration of database lock will take place so that it can be confirmed that all important actions have been properly performed. In addition, prior to database lock, and prior to the initiation of any statistical analysis activities a comprehensive statistical analysis plan (SAP) will be drafted. The SAP will also include information regarding the statistical software(s) to be used for the analysis of the study data and any data imputation methods that may be applied.

9.8 DATA ANALYSIS

9.8.1 Main Analysis

The objective of this registry is neither to confirm nor to reject any predefined hypothesis; therefore the nature of the statistical analyses will be exploratory and descriptive.

Continuous variables will be listed as median with interquartile and other percentages, and as mean value with standard deviation (SD), along with minimum and maximum values (depending on the underlying distribution). Categorical values will be listed as absolute and relative frequencies. All events during follow up will be described as incidence rates with 95% confidence interval (CI).

Stratified analyses will be performed among newly diagnosed patients (< 6 months) as well as patients that were diagnosed in the past (>= 6 months). In case of conflicting results those of the newly diagnosed will be the decisive. Due to limited number of patients and population heterogeneity, no comparison between treatments can be done and no causal relationship conclusion can be derived (no hypothesis testing). Statistical analyses will be performed with IBM SPSS Statistics (Version 19.0).

If it was not avoidable to select patients from sites with other ongoing registries, patients enrolled in other registries in parallel need to be analyzed separately. In case of difference the results for the BI registry patients are decisive.

[redacted]

9.9 QUALITY CONTROL

In order to ensure the quality and integrity of data throughout the course of the study, proper quality control mechanisms and methods will be applied.

eCRF files from each participating site will be stored in CD-ROMs after completion of the study and will be distributed to the participating sites.

The investigators will be provided with a folder/file by the authorized representative of the study, in which they will be required to keep and store all study related documents. All study documents will be stored in this file by the Investigator. The contents of this file/folder may be subjected to audit/inspection by an authorized auditor, regulatory authorities or Institutional Review Boards (IRBs)

[redacted] may conduct quality control visits of the study protocol and all related regulatory and BI procedures.

The Sponsor or designee (contracted CRO) will assure database quality by reviewing the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

9.10 LIMITATIONS OF THE RESEARCH METHODS

The basic limitations of the study relate to the general limitations that concern non - interventional studies. Since this study is a non - interventional study, it could be possible that different parameters which were not assessed and thus remain unknown, might lead to overestimating/underestimating/non-detection of differences of specific patients' characteristics. Selection bias on the patient level will be minimized by consecutive enrollment. Survival in IPF cohort studies is affected by the clinical characteristics and the related baseline patient conditions, as well as by the time interval between the diagnosis and the inclusion of the patient in the protocol. Patients that have been long diagnosed (at least more than 6 months before entering the study) with IPF and are included in the registry may be more likely to have a relatively more stable disease and/or better response in IPF management compared to the newly diagnosed patients; however, given the disease progression they will be in different disease stages. In this registry it will be possible to differentiate based on disease duration.

In case patient is lost to follow up, every effort will be made to contact the patient, keep him/her involved and if possible inquire about the reason of loss to follow-up. In order to assess the effect of loss to follow-up, percentages of dropouts will be summarized and patients will be characterized and compared to the remaining patients.

No re-evaluation of patients in this study is initially foreseen, something, that can lead to the conclusion that patients with overlapping diagnoses (like fibrosing interstitial pneumonia of unknown cause) have been included in the study, thus depicting the difficulties in differential diagnosis in clinical practice. However, given the fact that the participating sites are reference centers for IPF, and considering the eligibility criteria that apply for this study, the expected bias might be low.
The study is going to provide evidence regarding the situation in the IPF reference centers which are University Pulmonology Clinics and Pulmonology Clinics at Hospitals of Public Setting that follow up about 70%-80% of IPF patients in Greece.

Given the small numbers and the heterogeneous population no comparisons and causal associations can be assessed.

9.11 OTHER ASPECTS

Any other aspect of the research method not covered by the previous sections.

9.11.1 Data Quality Assurance

Monitoring visits will be performed to all participating sites, especially the ones that follow up large number of patients. During follow up visits the Study monitor will verify the documentation of the informed consent and will perform source data verification with the patient's medical records.

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

9.11.2 Study Records

The individual patient's Case Report Forms (CRFs) will be provided by the sponsor via an electronic data collection system (EDC).

Every doctor will have a study folder containing:

- The registry contract between the physician and [redacted].
- The protocol
- The patient identification list (not allowed to be used off site)
- An approval letter by the Scientific Committee/Ethics Committee for the specific site
- Informed consent forms
- eCRF Sample printouts

9.11.2.1 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.
For eCRFs all data must be derived from source documents.

9.11.2.2 Direct Access to Source Data and Documents

The investigator / institution will permit study-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) / Clinical Monitor Local (CML) and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 9.11.2.

9.11.2.3 Storage of Records

Patient's files and other source documents must be kept for the maximum time period permitted by the hospital/institution or as defined below. The investigator must consult with the sponsor in case they wish to transfer the files to a third party, move them to a different location or if they are not capable of maintaining them for the defined period.

The investigator should keep the study files (e.g. source documents like medical files, contracts, electronic files and signed informed consent forms) for as long as it is defined by the applicable laws and regulations. The sponsor is responsible for maintaining the documents for at least 15 years. The archived data can be kept in electronic form so long as there are available backup copies in printed form, if it is required.

The participating sites are responsible for the archiving of the necessary documents/evidence for 15 years at least or for as long as it is required by the local legislation. Completion of study

9.11.2.4 Completion of the Study

The Institutional Review Board (Scientific/Administrative Board) in each participating hospital center needs to be notified about the end of the study (last patient out) or early termination of the study, unless it is differently required by the national regulations that govern the conduct of such studies in case these regulations have been amended until the completion of the study.

10. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report, either interim or final.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This study will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Competent Authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

More specifically, according to national regulatory requirements, both the protocol and the informed consent form (ICF) must be submitted to the Institutional Review Board (Scientific/Administrative Board) of the participating hospitals in order to be granted approval. The Scientific/Administrative Board of the participating hospitals must approve any amendment to the protocol or the ICF before the implementation of the amendment or the use of ICF, according to local regulations. The present non – interventional study will be conducted according to the applicable national regulatory requirements that govern the conduct of such clinical trials.

The informed consent form (ICF) will be provided to the study centers in the Greek language. It is the responsibility of the treating physician in the study center to receive the voluntary informed consent form from the patient (or their authorized representative) according to the national ICH/GCP guidelines and the regulatory and legal requirements for participation in the registry before entering any patient data in the eCRF.

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the study records. A signed copy of

the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorized monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

10.2 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

Patient's private data are going to be used by Boehringer Ingelheim and will be kept according to the requirements of the EU Data Protection Directive (95/46/EC) [22]guidelines and the national legislation regarding protection of private data. Data will be collected with the use of key codes. The identification codes will be used instead of patient names in order to protect patient identities when referring to registry data. The level of disclosure should also be explained to the patient.

Only authorized staff (hospital staff, sponsor representatives including monitors, authority representatives) will have access to patient's private data e.g. original source documents (medical records). The patient will agree to this specifically by providing informed consent and the appropriate statement will be included in the Informed Consent Form (ICF).

The physician must comply with the confidentiality policy as it is defined within the Registry Contractual Agreement. The physician will comply with the Protocol that has been approved by the Scientific Board/Ethics Committee. The physician is responsible for the conduct of all registry aspects in the study site and validates the integrity of all forwarded to the sponsor data with their signature.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Adverse Event of Special Interest (AESI)

No AESIs have been defined for this study.

11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of Nintedanib. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the (e)CRF from signing the informed consent onwards until the end of the study:

- all ADRs related to Nintedanib, taken for idiopathic pulmonary fibrosis (serious and non-serious),
- all AEs with fatal outcome in patients exposed to Nintedanib, taken for idiopathic pulmonary fibrosis

All ADRs , including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:
- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced

- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Nintedanib for idiopathic pulmonary fibrosis , the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study to the [redacted] at [redacted]

Type of Report	Timeline
All **serious ADRs** associated with Nintedanib, taken for idiopathic pulmonary fibrosis	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Nintedanib, taken for idiopathic pulmonary fibrosis	immediately within 24 hours
All **non-serious ADRs** associated with Nintedanib, taken for idiopathic pulmonary fibrosis	7 calendar days
All **pregnancy monitoring** forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form. The NIS AE form and Pregnancy Monitoring Forms should be submitted to the [redacted] at [redacted] For details regarding Pregnancy Monitoring Forms, please refer to Section 11.2, paragraphs entitled, "Pregnancy" and "Expedited Reporting of AEs and Drug Exposure During Pregnancy."

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than Nintedanib taken for IPF, according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Participating physicians and Boehringer Ingelheim will be informed on the progress and status of the IPF registry on a regular basis. An Annual Report will be issued that contains a section on project management (recruitment status, information on technical and administrative issues) and tabular listings of data. Further, meetings of the National Scientific Committee as well as investigator meetings are planned (preferably in the context of major Pulmonology Meetings).

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

Following database lock, a final report that summarizes the tables of the analysis and explanatory text will be written by the Data Management. Data management according to our contractual agreement will prepare a final Study Report which will be used as a basis for the final Report that will be written internally. After approval from the members of the National Scientific Committee and the sponsor, a final version will be generated that may be used for regulatory purposes, but also as basis for the publications of the registry. Further, the results from the interim analyses will be available for abstracting/publishing in local or international conferences or scientific meetings.

Every effort will be made, given the collected data, in order to produce scientific publications that will in turn contribute to better care for IPF patients and justify the scientific effort. The publication strategy and the authors' list will be agreed between the [redacted] of [redacted] and the participating investigators. [redacted] will be the official owner of all collected date and results. Every study publication should be consistent with BI's publication policy and guided by the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals of the International Committee of Medical Journals (ICMJE) [24].

This study together with the results will be posted to the internet platform Clinicaltrials.gov (CT.gov), in the EU electronic register of post-authorization studies -ENCEPP (www.encepp.eu/encepp_studies/indexRegister.shtml) and in the platform of Non - Interventional Study Registries [Dilon (www.dilon.sfee.gr)] according to local requirements. This webpage is for the electronic registry and is part of the Hellenic Association of Pharmaceutical Companies (SFEE) website.

13. REFERENCES

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13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Not Applicable

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Note: Page number(s) refer to the first page number of the relevant Section.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection	☒	☐	☐	21
1.1.2 End of data collection	☒	☐	☐	21
1.1.3 Study progress report(s)	☐	☐	☒	-
1.1.4 Interim progress report(s)	☐	☐	☒	-
1.1.5 Registration in the EU PAS register	☐	☐	☒	-
1.1.6 Final report of study results.	☒	☐	☐	21

Comments:

1.1.3 → Not required according to national requirements for non -interventional studies
1.1.4 → Not required as no interim analysis of data is scheduled
1.1.5 → Not required as this study is not considered PASS

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**

2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	22 & 25
2.1.2 The objective(s) of the study?	☒	☐	☐	26
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	28
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	-
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	-

Comments:

2.1.4 & 2.1.5 → This study is not intended for hypothesis testing and will mainly use descriptive statistical methods. Any performed analysis will be of investigational nature.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	27
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☒	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

3.2 & 3.3 → As explained in section 2 no hypothesis testing is going to be performed therefore no specific effects or endpoints are defined.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	28
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	28
4.2.2 Age and sex?	☒	☐	☐	28
4.2.3 Country of origin?	☒	☐	☐	28
4.2.4 Disease/indication?	☒	☐	☐	28
4.2.5 Co-morbidity?	☒	☐	☐	-
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	28

Comments:

4.2.6 → Seasonal fluctuation and form is not applicable in this study and does not apply to the population of the study and the disease under investigation.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☐	☒	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

5.1, 5.2, 5.3, 5.4 & 5.5 → This study is a descriptive epidemiological Study that does not investigate the effect of specific exposure in order to test a hypothesis.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

N/A

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

7.1 & 7.2 → No confounders or effect modifiers are discussed since no hypothesis testing or assessment of effects is being performed.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	32, 36
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	36
8.1.3 Covariates?	☒	☐	☐	33

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	32,38
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	32-38
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	33
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	37

Comments:

8.3 → No codification system is applied.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☒	☐	36

Comments:

9.1→ The number of included patients as well as the duration of the Study is not defined by an official calculation of the sample size as the objective of the observational study is not to confirm or reject any predefined assumptions.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	38
10.3 Are descriptive analyses included?	☒	☐	☐	38
10.4 Are stratified analyses included?	☒	☐	☐	38
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

10.1 → No excess risks are expected due to the design of the non - interventional observational study that aims in describing everyday clinical practice. 10.5, 10.6 → No methods for adjusting for confounding or addressing effect modification are scheduled due to the fact that no hypothesis testing or assessment of effects is being performed.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☒	☐	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	37
11.3 Are methods of quality assurance described?	☒	☐	☐	40
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	40
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	-

Comments:

11.1 → Since this is an observational study where the duration is not defined by an official calculation of the sample size, the objective is to collect data from IPF patients during their participation in the study. 11.5 → The study design does not require an independent review of the results.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	39
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	39
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	36
12.3 Does the protocol address other limitations?	☒	☐	☐	39

Comments:

N/A

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	42
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	-
13.3 Have data protection requirements been described?	☒	☐	☐	43

Comments:

N/A

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	13

Comments:

N/A

Section 15: Plans for communication of study results		**Yes**	**No**	**N/A**	**Page Number(s)**
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	48
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	48

Comments:

N/A

ANNEX 3. ADDITIONAL INFORMATION

OUTCOME	DEFINITION
Mortality	a) Date of death b) Cause of death a. Related to IPF i. Respiratory failure: Is the consequence of lung failure leading to impaired gas exchange; that is, hypoxemia and/or hypercapnia ii. Acute exacerbation of IPF (see definition below) iii. Other related to IPF (please specify) b. Comorbid condition (please specify): i. Coronary heart disease ii. Cerebrovascular disease iii. Pneumonia/respiratory infection (see definition below) iv. Pulmonary embolism (see definition below) v. Pulmonary hypertension or Pulmonary arterial hypertension/right heart failure (see definition below) vi. Lung cancer (see definition below) c. Other cause (please specify) d. Unknown
Acute exacerbation of IPF	a) Previous or concurrent diagnosis of idiopathic pulmonary fibrosis b) Unexplained worsening or development of dyspnea within 30 days c) HRCT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern d) No evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage e) Exclusion of alternative causes, including: a. Left heart failure b. Pulmonary embolism c. Identifiable cause of acute lung injury
Myocardial infarction	a) In patients **not** undergoing PCI or CABG: A patient has to fulfil either the criteria: a. Development of significant Q-waves in at least 2 adjacent ECG leads. Or at least 2 of the following three criteria:

OUTCOME	DEFINITION
	b. Typical prolonged severe chest pain of at least 30 min c. ECG changes suggestive of myocardial infarction including ST-changes of T-wave inversion in the ECG). d. Elevation of troponin or CK-MB_1 to more than upper level of normal (ULN) or, if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level. b) After PCI (within 24 h) Elevation of troponin or CK-MB1 to more than 3xULN or, if CK-MB is elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or development of significant Q-$waves_2$ in at least two adjacent ECG leads. c) After coronary artery bypass grafting (within 72 h) Elevation of CK-MB1 to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-$waves_2$ in at least two adjacent ECG leads. 1 Total CK if CK-MB was not available 2 A new Q-wave with a duration of at least 0.04 seconds and a depth of more than a quarter of the amplitude of the corresponding R-wave, in at least 2 adjacent leads
CNS Infarction	a) Ischemic stroke b) Stroke caused by intracerebral hemorrhage c) Stroke caused by subarachnoid hemorrhage d) Stroke caused by cerebral venous thrombosis e) Stroke NOS f) Silent CNS infarction g) Silent cerebral hemorrhage
Other Arterial Thromboembolic events (excl. AMI, CNS Infarction, and Pulm embolism)	a) Acute limb ischemia b) Acute mesenteric ischemia c) Renal infarction d) Other (free text)
Deep vein thrombosis	Confirmed by - Ultrasound (dd-mm-yy) - Venography (dd-mm-yy) and Clinical presentation, i.e symptomatic/asymptomatic (yes-no-unknown)(such as leg pain, swelling, tenderness of the calf lower extremity) and arm discomfort - Edema, dilated venous collateral and discoloration (lower extremity) - no clinical symptoms or signs

OUTCOME	DEFINITION
Hemorrhage	a) Location: a. Gastrointestinal hemorrhage b. Intracranial hemorrhage c. Rectal hemorrhage d. Epistaxis e. Hemorrhage NOS b) Severity: a. Major bleeding, defined as meeting one or more of the following criteria): i. Overt bleeding associated with a reduction in hemoglobin of at least 20 grams per liter or leading to a transfusion of at least 2 units of blood or packed cells ii. Symptomatic bleeding in a critical area or organ: Intraocular, intracranial, intraspinal or intramuscular with compartment syndrome, retroperitoneal bleeding, intra-articular bleeding or pericardial bleeding iii. Life-threatening bleeding iv. Fatal bleeding b. Life-threatening bleeding, as defined as meeting one or more of the following criteria: i. Symptomatic intracranial bleed ii. Reduction in hemoglobin of at least 50 grams per liter iii. Transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of intravenous inotropic agents iv. Necessitated surgical intervention v. Fatal bleeding c) Circumstances: c. peri/postoperative d. accident/ injury e. other (please specify) f. unknown
Gastrointestinal perforation	a) Perforation of gastric ulcer b) Perforation of duodenal ulcer c) Perforation of small-intestine diverticulum d) Perforation of colon diverticulum e) Peritonitis as a complication of appendicitis f) Perforation as procedural complication (endoscopy),

OUTCOME	DEFINITION
	g) Others (please specify)
Pulmonary hypertension	a) Right-heart catheterization performed (mPAP>25 mmHg at rest) b) No RHC performed / Diagnosed by echocardiography or clinical diagnosis
Hospitalizations	a) Date entry b) Date discharge c) Hospitalization that requires mechanical ventilation (Yes/No) d) Hospitalization that includes ICU (Yes/No) e) Hospitalization due to respiratory cause (Yes/No) If Yes: a. Due to Acute exacerbation b. Due to IPF worsening other than Acute Exacerbation c. Other respiratory causes, NOS (e.g. pneumonia, pneumothorax,…) – please specify

ANNEX 4 ASSESSMENTS OF VARIABLES

Variable	**Categories**
Type of site	- Categorical: ・General practice/primary care ・Specialist office ・Community hospital ・University hospital ・Out-patient health care centre ・Anticoagulation clinics ・Other (please specify)
Age [years]	Calculated as the difference between date of birth and date of informed consent, convert to years (divided by 365.25) and lower truncated to the integer. Continuous and categorized as: - 40-44 - 45-54 - 55-64 - 65-74 - ≥75 - Unknown Additionally categorized as ≤65, >65 *<Please specify the category of reference if comparisons are foreseen e.g.:* ・ *- ≤65 years vs. >65 years old,*
Race	Categorized as: - American Indian or Alaska Native - Asian - Black or African American - Native Hawaiian or other Pacific Islander - White - Other Not reported
Gender	Categorized as: ・Male Female
Smoking status	- Categorized as: Never / Past / Current / Unknown For the Past/Current, specify packs/year and for Past (number of years smoking one pack per day equivalent)
Drugs of abuse	- Categorized: ・ Alcohol consumption: Drinker/ex-drinker/non-drinker/unknown

Variable	Categories
	· Cocaine consumption: Never / Past / Current / Unknown Other,(please specify)
Family history of pulmonary fibrosis	- Categorized as: Yes/No/Unknown
Environmental and occupational exposures	- Any exposure ticked in this category (Yes/No/Unknown): · Metal dusts (brass, lead, and steel) · Wood dust (pine) · Farming · Raising birds · Hair dressing · Stone cutting/polishing · Asbestos · Solvents
Exposure to drugs associated with IPF	- Any exposure ticked in this category (Yes/No/Unknown): · Amiodarone · Bleomycine · Nitrofurantoine · Methotrexate - Gold salts
Exposure to viral infection with potential association with IPF	- Serum antibodies for (Positive/Negative/not available) · Ebstein-Barr Virus · Hepatitis C virus Other positive (please specify)
Diagnostic procedures that were used during diagnostic workout	- Date: DD-MMM-YYYY - High-Resolution Computed Tomography [HRCT] - UIP pattern - Possible UIP pattern - Inconsistent UIP pattern - Not available - Histology (lung biopsy) - UIP pattern - Probable UIP pattern - Possible UIP pattern - Inconsistent with UIP or non-classifiable - Not available
Date when IPF was diagnosed	- Format: DD-MMM-YYYY
Lab values	At enrolment, to exclude connective tissue disease (positive/negative/not performed/unknown/performed but missing value) and value (units):

Variable	Categories
	· Rheumatoid factor · Anti-cyclic citrulinated peptide (anti-CCP) · Anti-nuclear antibodies (ANAs) · Scl-70 · SS-A · SS-B · Other biomarker of autoimmune disease (please specify)
Vital signs and physical examination	- Continuous and categorical, as appropriate. - Categorized as Yes/No/Unknown and further categorized as (examples) : · Heart rate (BPM) · Blood pressure (mmHg) · Weight · Height · Date: DD-MMM-YYYY
Pulmonary function testing	- Continuous · FVC (mL, % pred) · VC (mL, % pred) · TLC (mL, % pred) · DLCO (mmol/min/kPa, % predicted Hb corrected) · FEV1 (mL, % pred) - Further categorized as: Yes/No/Unknown Date of pulmonary function testing: DD-MMM-YYYY
Biomarkers of autoimmune disease	- Lab values of interest include (continuous): · Hb (g/dL), · AST (µg/L) · ALT (µg/L) · Total bilirubin (mg/dL) · BNP (ng/L) · NT pro-BNP (ng/L) - Further categorized as: Yes/No/Unknown · Date: DD-MMM-YYYY
Bleeding risk	- Genetic predisposition (please specify) - Gastrointestinal ulcers - Major injury or surgery · Use of anticoagulants
Thrombotic risk	· Genetic predisposition (please specify)
Concomitant medications, please assess for each start/stop date and dose	Any co-medication ticked in this category (Yes/No/Unknown) · Corticosteroids · NAC · Azathioprine · Cyclophosphamide

Variable	Categories
	· Cyclosporine A · Other immuno-suppressant (e.g. mycophenolate mofetil) · Pirfenidone · Anticoagulant · Vit-K antagonist · Heparin · NOAC · Other · High-dose antiplatelet therapy · GERD medication · PDE-5 inhibitor · Endothelin receptor antagonist · Long-term Oxygen therapy · Listed for lung transplantation · NSAIDs · Hormonal contraceptives · Hormone replacement therapy · Anti-VEGF drugs
Current participation in pulmonary rehabilitation program	- Categorized as: Yes/No/ Unknown
Listing for or participation in lung transplantation	- Categorized as: Yes/No/Unknown - Date since when: DD-MMM-YYYY
Vital status	Categorized as: Yes/No/Unknown ·
Pulmonary function testing	- Continuous · FVC (mL, % pred) · VC (mL, % pred) · TLC (mL, % pred) · DLCO (mmol/min/kPa, % predicted Hb corrected) · FEV1 (mL, % pred) - Further categorized as: Yes/No/Unknown · Date of pulmonary function testing: DD-MMM-YYYY
Hospitalizations	- Categorized as: Yes/No/Unknown If yes: further categorized as: · with/without ER use · with/without ICU use · with/without mechanical ventilation · with/without ambulance use - Date of hospitalizations: · Known/Unknown · If known: DD-MMM-YYYY

Variable	Categories
	- Discharge or death date: ・ Known/Unknown ・ If known: DD-MMM-YYYY

ANNEX 5. COMMORBIDITIES OF INTEREST (RECORDER WITH START, AND IF APPLICABLE STOP DATE)

- Previous Haemorrhages
- Cardio and cerebrovascular comorbidities: Arterial hypertension, coronary artery disease (CAD), myocardial infarction (MI), congestive heart failure (CHF), CNS Infarction, transient ischaemic attack (TIA), peripheral artery disease, atrial fibrillation, deep venous thrombosis, pulmonary embolism, pulmonary hypertension
- Respiratory comorbidities: chronic obstructive pulmonary disease (COPD), emphysema (radiologic), asthma, pneumonia, obstructive sleep apnea
- Renal comorbidities: chronic renal failure (see definition in Section14.2)
- Hepatic comorbidities: chronic hepatic failure, cirrhosis
- Gastrointestinal comorbidities: gastroesophageal reflux disease (GERD), gastric ulcer, appendicitis, abdominal surgery, inflammatory bowel disease (e.g. Crohn's disease, ulcerative colitis), GI cancer, diverticulitis, superior mesenteric artery syndrome
- Metabolic comorbidities: T2/T1 diabetes mellitus, hyperlipidaemia, hypothyroidism
- Neoplasms: lung, liver, stomach, colorectal, breast and oesophageal, prostate and cervix cancer
- Depressive disorder, anxiety disorder.

ANNEX 6. HIGH RESOLUTION COMPUTED TOMOGRAPHY CRITERIA FOR USUAL INTERSTITIAL PNEUMONIA PATERN (UIP) [1]

UIP Pattern (All Four Features)	Possible UIP Pattern (All Three Features)	Inconsistent with UIP Pattern (any of the Seven Features)
Subpleural, basal predominance Reticular abnormality Honeycombing with or without traction bronchiectasis Absence of features listed as inconsistent with UP (see column 'Inconsistent with UIP Pattern', on the right)	Subpleural, basal predominance Reticular abnormality Absence of features listed as inconsistent with UP (see column 'Inconsistent with UIP Pattern', on the right)	Upper or mid-lung predominance Peribronchovascular predominance Extensive ground glass abnormality (extent>reticular abnormality) Profuse micronodules (bilateral, predominantly upper lobes) Discrete cysts (multiple, bilateral, away from areas of honeycombing) Diffuse mosaic attenuation/air-trapping (bilateral in three or more lobes) Consolidation in bronchopulmonary segment(s)/lobe(s)

ANNEX 7. HISTOLOGICAL CRITERIA FOR UIP PATERN IN LUNG BIOPSY [1]

UIP pattern (all 4 criteria)	**Probable UIP pattern**	**Possible UIP pattern (all 3 criteria)**	**Not UIP pattern (any of the 6 criteria)**
Evidence of marked fibrosis/ architectural distortion,±honeycombing in a predominantly subpleural/paraseptal distribution Presence of patchy involvement of lung parenchyma by fibrosis Presence of fibroblast foci Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column 'Not UIP pattern')	Evidence of marked fibrosis/ architectural distortion,±honeycombing Absence of either patchy involvement or fibroblastic foci, but not both Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column 'Not UIP pattern') Or Honeycomb changes only‡	Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation Absence of other criteria for UIP (see 'UIP Pattern column') Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (see fourth column) 'Not UIP pattern')	Hyaline membranes* Organizing pneumonia*† Granulomas† Marked interstitial inflammatory cell infiltrate away from honeycombing Predominant airway centered changes Other features suggestive of an alternate diagnosis

*Can be associated with acute exacerbation of idiopathic pulmonary fibrosis.
† An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern .
‡This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided. By using HRCT the pre-operative targeting of biopsy sites is performed away from these areas.

APPROVAL / SIGNATURE PAGE

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