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Non-interventional Study Protocol

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Research question and objectives:	Long-term data on the natural course of IPF in Italy are scarce. Further, there is limited information on IPF in terms of patient characteristics and disease management. The purpose of the present study is to evaluate the characteristics, management and clinical course of patients with IPF as treated under real-world in Italian Pulmonary Centres, in terms of symptoms, lung function and exercise tolerance during 12 months of observation.

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	In particular, the study aims to provide information on disease characteristics and treatment modalities (at enrolment) and on disease progression, HRQoL and health care sector-related costs according to the Italian National Health Service (INHS) point of view (during 12 months of observation). **OBJECTIVES** ***Primary objective*** 1. In a sample of Italian IPF diagnosed patients, to describe the clinical course during 12 months of observation, in terms of: • symptoms • lung function (VC, FVC, FEV1, TLC, DLCO, pO2, pCO2) • exercise tolerance (6-minute walk distance test).
Country(-ies) of study:	***Secondary objectives*** 1. Description of characteristics of IPF patients at enrollment in terms of: o key (socio-) demographic data o IPF risk factors, comorbidities o IPF disease severity and manifestation (including lung function, cardiopulmonary exercise testing and/or exercise capacity if available, laboratory values) o Methods used for IPF diagnosis o IPF treatment modalities (detailed information on prescribed drugs and dose; non-pharmacological treatment; lung transplantation) 2. To describe the frequency of exacerbations during 12 months of observation. 3. To describe HRQoL variation, measured with SGRQ, EuroQol (EQ) 5-dimension 5-level (EQ-5D-5L) descriptive system and EQ VAS, during 12 months of observation. 4. To describe health care sector-related costs from diagnosis up to the end of 12-months follow-up according to the Italian National Health Service (INHS) point of view.
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2. LIST OF ABBREVIATIONS

AE	Adverse Event
ALAT	Latin American Thoracic Association
ATS	American Thoracic Society
BAL	BronchoAlveolar Lavage
BITSPA	Boehringer Ingelheim Italy S.p.A.
BMI	Body Mass Index
CI	Confidence Interval
CNS	Central Nervous System
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
DLCO	Diffusion Lung Capacity for carbon monoxide
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D-5L	EuroQol 5-dimension 5-level
ERS	European Respiratory Society
FVC	Forced vital capacity
FEV1	Forced expiratory volume in the 1st second
GCP	Good Clinical Practice
GERD	Gastroesophageal Reflux Disease
GPP	Good Pharmacoepidemiology Practice
HRCT	High Resolution chest Computer Tomography
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
INHS	Italian National Health Service
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
ISF	Investigator Site File
JRS	Japanese Respiratory Society
LCM	Local Clinical Monitor
LHA	Local Health Authority
LTOT	Long-Term Oxygen Therapy
LTx	Lung Transplantation
MAH	Market Authorization Holder

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MedDRA	Medical Dictionary for Drug Regulatory Activities
MMF	Mycophenolate MoFetil
MST	Medical Subteam
NIS	Non-interventional Study
p.o.	per os (oral)
PCC	Protocol Challenge Committee
PRO	Patient Related Outcomes
q.d.	quaque die (once a day)
QoL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	subcutaneous
SGRQ	St. George's Hospital Respiratory Questionnaire
SPC	Summary of Product Characteristics
SD	Standard Deviation
t.i.d.	ter in die (3 times a day)
VC	Vital Capacity
TLC	Total Lung Capacity
UIP	Usual Interstitial Pneumonia

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3. RESPONSIBLE PARTIES

List of all main responsible parties, including the principal investigators who signed this page, will be kept in a stand-alone document to be listed in Annex 1 and it will be available upon request.

SIGNATURE PAGE

This study protocol has been carefully reviewed and agreed upon by:

1/7/2015
Date, signature

Associate Medical Advisor
Boehringer Ingelheim
Milano

1/07/2015
Date, signature

For Contract Research Organization,

Clinical Operation

26/06/2015
Date, signature

Statistician

26/6/15
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Name of company: Boehringer Ingelheim			
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Protocol date: 26th June 2015	**Study number:** 1199.262	**Version/Revision:** 1.0	**Version/Revision date:** 26/06/2015
Title of study:	IPF Italian observational study		
Rationale and background:	Idiopathic Pulmonary Fibrosis (IPF) is a rare disease of unknown etiology that is characterized by progressive fibrosis of the interstitium of the lung, leading to decreasing lung volume and progressive pulmonary insufficiency [1][2], presenting more frequently in men than in women and is usually diagnosed in people over 50 years of age, particularly those with a history of cigarette smoking [2]. Idiopathic Pulmonary Fibrosis is usually associated with a poor prognosis: the clinical course of IPF can be unpredictable [3][4]. IPF progression is associated with an estimated median survival time of 2 to 5 years following diagnosis [1][2]. The 5-year survival for IPF ranges between 20% and 40% [4]. Recognizing IPF in clinical practice can be challenging as symptoms often appear similar to those of more common diseases. This contributes to delay the diagnosis which is usually made 6 to 24 months after initial symptoms [7][8]. An earlier diagnosis of IPF is a prerequisite for earlier treatment and, potentially, improvement of the long-term clinical outcome [1]. A multidisciplinary approach involving a pulmonologist, radiologist and pathologist expert in interstitial lung disease has been shown to improve the accuracy of IPF diagnosis[2][5][6]. A Multidisciplinary Consensus Statement on the Idiopathic Interstitial Pneumonias published by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2000 proposed specific major and minor criteria for establishing the diagnosis of IPF [2]. However, in 2011, new simplified and updated criteria for the diagnosis and management of IPF were published by the ATS, ERS, together with the Japanese Respiratory Society (JRS) and Latin American Thoracic Association (ALAT) [2]. Currently, a diagnosis of IPF requires: • Exclusion of other known causes of Interstitial Lung Disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity). • The presence of a Usual Interstitial Pneumonia (UIP) pattern on High Resolution chest Computed Tomography (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. It is possible to make the diagnosis of IPF by HRCT alone, obviating the need for surgical lung biopsy [1][2]. Except lung transplantation, that in a small portion of patients provides a chance of long-term survival, there is currently no therapy that reverses or cures the lung damage. Conventional IPF treatments such as corticosteroids, cyclophosphamide, cyclosporine and azathioprine are not approved treatments for IPF, and their efficacy is questionable. Other treatments with anti-fibrotic action are currently being investigated. Pirfenidone has been the first product to receive EU approval and recently approved in USA, as a treatment for mild to moderate IPF because in these cases it significantly reduces the decline of lung function.		

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	Nintedanib, a tyrosine kinase inhibitor has been recently approved in EU and in USA for the treatment of patients with IPF. Nintedanib has shown to have a clinical benefit on slowing of deterioration in lung capacity with evidence of reduction of the rate of decline in lung function as indicated by absolute volume FVC. Finally oxygen therapy and non pharmacological treatment, such as pulmonary rehabilitation are usually recommended. Dyspnea and cough are hallmark symptoms of IPF, and both appear to have important effects not only on Health-Related Quality of Life (HRQoL) but also on survival [15]. IPF patients have unpredictable acute exacerbations, which could occur even with mild physiological impairment. Moreover IPF patients experience depressive symptoms, which are correlated to HRQoL impairment and fatigue. HRQoL is further worsened as daily activities become limited and patients grow increasingly oxygen dependent, debilitated, and dependent on others [15]. Not only prevalence of IPF is higher in men and in the older age groups, but also burden and cost of disease varies accordingly [14]. In fact, higher increase in hospital admissions was found in men and older age groups by Navaratnam and colleagues [14]. They also estimated that the financial burden from IPF inpatient care alone in England is currently £16 million and will be almost £20 million by 2020.
Research question and objectives:	Long-term data on the natural course of IPF in Italy are scarce. Further, there is limited information on IPF in terms of patient characteristics and disease management. The purpose of the present study is to evaluate the characteristics, management and clinical course of patients with IPF as treated under real-world in Italian Pulmonary Centres, in terms of symptoms, lung function and exercise tolerance during 12 months of observation. In particular, the study aims to provide information on disease characteristics and treatment modalities (at enrollment) and on disease progression, HRQoL and health care sector-related costs according to the Italian National Health Service (INHS) point of view (during 12 months of observation). **OBJECTIVES** ***Primary objective*** 1. In a sample of Italian IPF diagnosed patients to describe the clinical course during 12 months of observation, in terms of: • symptoms • lung function (VC, FVC, FEV1, TLC, DLCO, pO2, pCO2, SaO2, PaO2 and PaCO2 at rest) • exercise tolerance (6-minute walk distance test). ***Secondary objectives*** 1. Description of characteristics of IPF patients at enrollment in terms of: ○ key (socio-) demographic data ○ IPF risk factors, comorbidities ○ IPF disease severity and manifestation (including lung function, cardiopulmonary exercise testing and/or exercise capacity if available, laboratory values) ○ Methods used for IPF diagnosis ○ IPF treatment modalities (detailed information on prescribed drugs and

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	dose; non-pharmacological treatment; lung transplantation) 2. To describe the frequency of exacerbations during 12 months of observation. 3. To describe HRQoL variation, measured with SGRQ, EuroQol (EQ) 5-dimension 5-level (EQ-5D-5L) descriptive system and EQ VAS, during 12 months of observation. 4. To describe health care sector-related costs from diagnosis up to the end of 12-month follow-up according to the Italian National Health Service (INHS) point of view.
Study design:	This is an observational, multicenter prospective cohort study based on newly collected data, involving 20 Italian Pulmonary Centers highly experienced in the disease management of IPF. The enrolment period will last 18 months. During this period, about 200 consecutive patients will be included in agreement with the inclusion/exclusion criteria. Patients will be followed up for 1 year, with 3 intermediate evaluations after 3 (+/-1), 6 (+/-1) and 9 (+/-1) months from baseline (such visits are referred as being the current clinical practice in Italy for IPF patients management). No treatment will be administered to the patients on the protocol basis, since this is an observational study and the assessment and treatment of the enrolled patients is based only on the investigators' clinical routine practice.
Population:	Patients newly diagnosed with IPF less than 3 months before the patient's inclusion visit referring to pulmonary centers will be consecutively enrolled according to the following criteria: *Inclusion Criteria* 1. Patients aged>=40 years 2. Written informed consent to both participation in the study and privacy 3. Physician diagnosed IPF during the last 3 months based upon recent ATS/ERS/JRS/ALAT guidelines 2011 (see Tables A1-A2 for HRCT and histology criteria): • 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 HRCT and surgical lung biopsy (see Tables A1-A2 for details) if available. 4. Patient with further follow-up possible with enrolling investigator during planned study period 5. Patients capable of discernment and able to read or write in Italian language. *Exclusion Criteria* 6. Inclusion in clinical trials or other IPF/ILD registries 7. Lung transplantation expected within the next 6 months 8. Pregnancy or breast feeding *Study-exit Criteria* 9. Inclusion in clinical trials 10. Consent withdrawal (from patient or legally accepted representative) 11. The patient was erroneously included in the study 12. Pregnancy or breast feeding 13. Any other reason as agreed to by the investigator and the BITSPA clinical

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monitor

Variables:

Study Visits	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
	Baseline	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4
Months	0	3 (+/-1)	6 (+/- 1)	9 (+/- 1)	12 (+/- 1)
Eligibility criteria Inclusion and exclusion criteria, Informed consent and privacy form	X				
Baseline information (Socio-)demographic variables: age, gender, race, body mass index, geographic location, educational degree, marital status, housing situation and employment status	X				
Potential IPF risk factors Cigarette smoking (including pack/years), environmental exposure, drug exposure, family history, other	X	X	X	X	X
Comorbidities Atherothrombotic disease including coronary heart disease, previous myocardial infarction, cerebrovascular disease, peripheral arterial disease, gastroesophageal reflux disease, pulmonary hypertension, emphysema, lung cancer, renal insufficiency	X	X	X	X	X
Baseline information on IPF First symptoms; date of first diagnosis; if performed, dates and results of HRCT, surgical lung biopsy, bronchoalveolar lavage	X				
IPF Symptoms Cough, Fatigue, Dizziness, Chest pain, Clubbing, Bibasilar crackles	X	X	X	X	X
Functional assessment Lung function test (VC, FVC, FVC % predicted, FEV1, TLC, DLCO, DLCO % predicted, pO2, pCO2, SaO2, PaO2 and PaCO2 at rest); 6-minute walk distance (if performed)	X	X	X	X	X
Exacerbations Onset and end date Description of management (if	X	X	X	X	X

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	available)					
	Pharmacological treatments related to both IPF and adverse events (drug, dosage regimen, start / end date or ongoing): Steroids, anticoagulants, immunomodulators (azathioprine, cyclophosphamide, MMF, etc), N-Acetylcysteine, Pirfenidone, Nintedanib	X	X	X	X	X
	Presence on listing for lung transplantation (yes/no)	X	X	X	X	X
	Non Pharmacological treatment - Pulmonary rehabilitation; - Long-Term Oxygen Therapy (liquid and/or concentrate).	X	X	X	X	X
	Health-care resource consumption related to both IPF and IPF-related adverse events: hospitalization (inward and day-hospital), emergency room access, specialist visits, General Practitioner visits, laboratory tests or examinations, imaging sessions, pharmacological and non-pharmacological treatments	X	X	X	X	X
	Patient Reported Outcomes Questionnaires/scales					
	HRQoL EQ-5D-5L descriptive system and EQ VAS; Saint George Respiratory Questionnaire (SGRQ)	X		X		X
	Adherence to therapy Morisky medication Adherence Scale 4 items (MMAS-4)	X		X		X
	Anxiety and Depression Hospital Anxiety and Depression Scale (HADS)	X		X		X
	Dyspnea Modified Medical Research Council Dyspnea Scale	X		X		X
	Survival Status		X	X	X	X
	Adverse Events and Adverse Drug Reactions description, onset and resolution date, relation with drugs, severity, seriousness.		X	X	X	X
	Clinical events CNS infarction, myocardial	X	X	X	X	X

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infarction, other arterial thromboembolic events, deep vein thrombosis, hemorrhage, gastrointestinal perforation, pulmonary hypertension)						

Visit 2 (3+/-1 month), Visit 3 (6+/-1 month) and Visit 4 (9+/-1 month) are referred as being the current clinical practice in Italy for IPF patients management.

Diagnostic Tools/Patient Reported Outcomes Questionnaires

- Modified Medical Research Council Dyspnea Scale (MMRC);
- Morisky medication Adherence Scale 4 items (MMAS-4);
- EuroQoL-5D 5L;
- Hospital Anxiety and Depression Scale (HADS);
- Saint George Respiratory Questionnaire (SGRQ).

The following procedures will be applied at each study visit according to routine clinical practice:

- Lung function test (VC, FVC, FEV1, TLC; DLCO; pO2, pCO2; SaO2, PaO2 and PaCO2 at rest);
- 6-minute walked distance test.

Data sources:

Data will be collected at baseline, 3, 6, 9 and 12-month follow up and the following questionnaire and scales will be administered to patients: Modified Medical Research Council Dyspnea Scale (MMRC); Morisky medication Adherence Scale 4 items (MMAS-4); EuroQoL-5D 5L; Hospital Anxiety and Depression Scale (HADS); Saint George Respiratory Questionnaire (SGRQ). (see Variables section for details).

Study size:

The sample size was determined on the basis of feasibility criteria. In fact, according to the volume of patients managed by the centers involved in this study, inclusion of 200 subjects (10 patients/center) with the characteristics defined at Inclusion/Exclusion criteria paragraphs is deemed reasonable for enrolment period (18 months).

An evaluation of the possible achievable precision of the estimates was performed considering the primary objective of the study and literature data, when available.

The primary objective of the study is to describe the clinical course during 12 months of observation, in terms of symptoms, lung function and exercise tolerance. Assuming a drop-out rate ranging from of 20% to 40% , the total number of evaluable patients at 12-month follow-up visit is expected to range between 120 and 160 subjects. Drop-out rate was hypothesized by considering mortality rate in IPF patients and natural drop-out from studies. Literature data about the clinical course of outcomes of interest in IPF patients in a real-life context are scanty. Nishiyama et al. [35] conducted a study on 93 IPF patients and assessed the pulmonary function. The mean (±SD) of FVC, FEV1, DLCO were 2.37 (±0.73) L, 1.93 (±0.57) L and 9.19 (±3.92) mL*min-1*mmHg-1 respectively. According to the data of a recently completed trial on patients with IPF by Swigris et al [37], the mean (±SD) baseline 6-min walked distance was 372.9 (±82.63) meters. Regarding the most common IPF symptoms, clubbing, dyspnea (evaluated by means of a mMRC score ≥2), crackles and cough frequencies are 43%, 44%, 67% and 73% respectively [34] [35].

Table 1 *shows the two-sided 95% confidence interval (CI) for expected frequency of IPF symptoms for a sample size n=120 and 160, using the large sample normal approximation [36].*

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	Expected frequency	95% CI	
IPF symptoms			
n=120			
Clubbing	43%	34.1%	51.9%
Dyspnea (mMRC score ≥2)	44%	35.1%	52.9%
Crackles	67%	58.6%	75.4%
Cough	73%	65.1%	80.9%
n=160			
Clubbing	43%	35.3%	50.7%
Dyspnea (mMRC score ≥2)	44%	36.3%	51.7%
Crackles	67%	59.7%	74.3%
Cough	73%	66.1%	79.9%

Table 2 shows the two-sided 95% CI for expected mean of FVC, FEV1, DLCO and 6-min walked distance for sample sizes of n=120 (drop out=40%) and n=160 (drop out=20%), assuming the SD reported in the table and the confidence interval is based on the large sample z statistic [36]. IPF is a degenerative disease, therefore it is expected a worsening of symptoms, lung function and exercise tolerance. However, a conservative evaluation was performed by taking into account the two-sided 95% confidence interval.

Table 2 *two-sided 95% CI of expected FVC, FEV1, DLCO and 6-min walked distance mean with sample sizes n=120 and 160. Cells are gray when the relative error - calculated as the ratio between 95% CI half-width and expected mean - is lower than 30%.*

	Expected mean	SD	95% CI	
n=120 (drop out=40%)				
FVC (L)	2.37	0.73	2.24	2.50
FEV1 (L)	1.93	0.57	1.83	2.03
DLCO (mL*min-1*mmHg-1)	9.19	3.92	8.49	9.89
6-min walked distance (m)	372.9	82.63	358.12	387.68
n=160 (drop out=20%)				
FVC (L)	2.37	0.73	2.26	2.48
FEV1 (L)	1.93	0.57	1.84	2.02
DLCO (mL*min-1*mmHg-1)	9.19	3.92	8.58	9.80
6-min walked distance (m)	372.9	82.63	360. 1	385.70

Data analysis:

The statistical analysis will be performed on all evaluable patients who enter the study and meet the inclusion criteria. Patients with missing values will not be excluded from the analysis, their data will not be replaced; frequency of missing data will be given for all analyzed variables.

Descriptive analysis will be composed of means, medians, quantiles, proportions (with their respective 95% confidence intervals, CI) and contingency tables according to the nature of the variables. As a dispersion measurements, the standard deviation and the interquartile range will be calculated. All events during follow-up will be described as incidence rates with 95% CI.

The study objectives will be evaluated as follows:

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Primary objective

To describe the clinical course of IPF during 12 months of observation

At each follow up visit the frequency of IPF symptoms (cough, fatigue, dizziness, chest pain, clubbing, bibasilar crackles) will be provided and the variation between visits will be described too mostly in terms of incident and worsening symptoms. Moreover, the score of the Modified Medical Research Council Dyspnea Scale for the evaluation of dyspnea at each follow up visit will be calculated together with the variation since baseline and between follow up visits.

The following outcomes will be also considered during the 12-month observation: lung function parameters (like VC, FVC, FEV1, TLC, DLCO, pO2, pCO2; SaO2, PaO2 and PaCO2 at rest) and patient's exercise capacity (evaluated by means of 6-minute walked distance test, if available). The outcomes will be described at each follow up by means of descriptive statistics and the variation between visits will be provided too.

Secondary objectives

#1 Description of IPF patients at enrollment (socio-demographic data, IPF risk factors, comorbidities, disease severity and manifestation, methods for diagnosis, treatment modalities)

IPF patients enrolled at baseline will be described in terms of socio-demographic variables (e.g. age, gender, race, body mass index, educational degree, and employment status) and potential IPF risk factors (such as smoking habits, environmental exposure, drug exposure, other factors).

The absolute and relative frequency (N, %) distributions of patients according to ongoing comorbidities (such as gastroesophageal reflux disease, pulmonary hypertension, emphysema, lung cancer, coronary heart disease, depression) will be also provided at baseline.

Treatment modalities will be described at each visit by means of frequency distribution of patients according to ongoing therapies for IPF; pharmacological (such as steroids, anticoagulants, immunomodulators, N-acetylcysteine, pirfenidone, etc..) and non-pharmacological (such as long term oxygen and pulmonary rehabilitation) therapies will be considered and described in terms of drug, dosage regimen and duration/number of sessions (including start and stop dates). The frequency of patients on listing for lung transplantation at baseline will be also provided.

The adherence to anti-IPF medications will be assessed too by means of the Morisky medication Adherence Scale 4 items (MMAS-4) scale considering evaluable patients with ongoing anti-IPF medications who have at least 3 out of 4 items of the scale filled-in [25,26,27]. The distribution of patients according to the four items of the scale will be also provided.

Finally, descriptive statistics of the Hospital Anxiety and Depression Scale (HADS) scores will be provided to describe patients' levels of anxiety and depression.

#2 To describe the frequency of exacerbations during 12 months of observation

The proportion of patients with at least one exacerbation after 12 months of observation will be computed as the ratio between the number of patients with one or more episodes of exacerbation occurred during 12 months of follow up over the total number of evaluable patients. Patients who drop-out without having exacerbations before the end of the study, will be considered in the denominator of the proportion of interest. The median number of episodes of exacerbation per patient will also be provided. Finally time to first exacerbation will be analyzed by Kaplan-Meier curves.

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	#3 To describe the HRQOL variation during 12 months of observation The descriptive statistics will be produced for EQ-5D-5L descriptive system index and VAS. Moreover, the difference of scores between baseline and available follow up visits will be calculated too. Similarly, the descriptive statistics of St. Georges Respiratory Questionnaire scores (symptoms, activity and impacts and total score) will be calculated. Graphs of mean HRQoL scores according to visits will also be provided to show the trend of variation, if any. ***#4 To describe health care sector-related costs during 12 months of observation*** In order to describe health care sector-related costs at diagnosis and from diagnosis up to the end of 12-month follow-up according to the INHS point of view, a two steps approach will be followed: (i) first of all the resource consumption since diagnosis will be collected or estimated and then (ii) a monetary value will be assigned to the collected or estimated resource consumption. (i) Health care resource consumption exclusively related to both IPF and IPF-related adverse events will be computed during observational period in terms of pharmacological and non-pharmacological treatments, number of (inward and day-hospital) hospitalizations, number of emergency room visits, number of General Practitioner visits, laboratory tests or examinations (spirometry, BAL, saturation), number of imaging sessions. Health care resources consumed during a three-month span of time between date of diagnosis and inclusion in the study will be retrospectively collected via an *ad hoc* section of the case report form (CRF) and/or estimated.(ii) In order to estimate the economic impact on health care sector-related costs of the above mentioned health services (hospital admissions, visits, treatments, examinations) consumption, a monetary value to each event recorded will be assigned, as defined by the Italian Ministry of Health through the tariff in force for outpatient setting [28]. The cost of hospitalization will be valued according to the most recent available diagnosis-related group (DRG) tariffs; finally pharmacological treatments will be costed at consumer price. All costs will be expressed in €. A monthly (or yearly) cost will be provided by taking into account patients according to duration of observation and parametrizing each patient to the 1-year observation period. Cost of Illness (COI) will be analyzed via descriptive statistics (mean; standard deviation; median; minimum and maximum). Non-parametric bootstrap method will be applied to COI data for calculating 95% confidence intervals.
Milestones:	• First patient in: December 2015 • Last patient in: May 2017 • Last patient out: May 2018 • Final study report: October 2018

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4. AMENDMENTS AND UPDATES

Any change or addition to the protocol requires a written protocol amendment that must be approved by BITSPA and all main responsible parties, the principal investigator and the relevant EC before implementation. Amendments only affecting administrative aspects of the study do not require formal protocol amendments or EC approval but the ECs have to be informed of such administrative changes.

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5. MILESTONES

The first patient enrolled in the study is expected in December 2015. The end of the data collection (including the follow-up period) is expected within May 2018, depending on the effective enrolment period necessary to collect data from two hundred patients.

Milestone	Planned Date
Start of data collection	31 December 2015
End of data collection	31 May 2018
Final report of study results:	31 October 2018

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6. RATIONALE AND BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a rare disease of unknown etiology that is characterized by progressive fibrosis of the interstitium of the lung, leading to decreasing lung volume and progressive pulmonary insufficiency [1][2], presenting more frequently in men than in women and is usually diagnosed in people over 50 years of age, particularly those with a history of cigarette smoking [2].

Several potential risk factors for the development of IPF have been identified. These include environmental and occupational exposures, tobacco smoking, comorbidities (in particular gastroesophageal reflux disease [GERD]), and genetic polymorphisms. The identification of risk factors for IPF is critically important as it may inform prevention strategies, early diagnosis, and novel therapies [16].

There is a strong association (prevalence of approximately 90%) between gastroesophageal reflux and IPF [17-20]. Moreover, although a causal relationship is unclear, it has been hypothesized that gastroesophageal reflux may be a risk factor for microaspiration, and this may be important in the pathogenesis and natural history of IPF [21].

IPF also appears to be more common in men compared to women, however, some postulate this may be due to sex differences in historical smoking patterns rather than an inherent sex-related risk for IPF [16].

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Idiopathic Pulmonary Fibrosis is usually associated with a poor prognosis: the clinical course of IPF can be unpredictable [3][4]. IPF progression is associated with an estimated median survival time of 2 to 5 years following diagnosis [1][2]. The 5-year survival for IPF ranges between 20% and 40% [4].

Recognizing IPF in clinical practice can be challenging as symptoms often appear similar to those of more common diseases. This contributes to delay the diagnosis which is usually made 6 to 24 months after initial symptoms [7,8]. An earlier diagnosis of IPF is a prerequisite for earlier treatment and, potentially, improvement of the long-term clinical outcome[1]. A multidisciplinary approach involving a pulmonologist, radiologist and pathologist expert in interstitial lung disease has been shown to improve the accuracy of IPF diagnosis[2][5][6].

A Multidisciplinary Consensus Statement on the Idiopathic Interstitial Pneumonias published by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2000 proposed specific major and minor criteria for establishing the diagnosis of IPF[2]. However, in 2011, new simplified and updated criteria for the diagnosis and management of IPF were published by the ATS, ERS, together with the Japanese Respiratory Society (JRS) and Latin American Thoracic Association (ALAT)[2]. Currently, a diagnosis of IPF requires:

- Exclusion of other known causes of Interstitial Lung Disease (ILD) (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
- The presence of a Usual Interstitial Pneumonia (UIP) pattern on High Resolution chest Computed Tomography (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.

It is possible to make the diagnosis of IPF by HRCT alone, obviating the need for surgical lung biopsy [1][2].

Except lung transplantation, that in a small portion of patients provides a chance of long-term survival, there is currently no therapy that reverses or cures the lung damage. Conventional IPF treatments such as corticosteroids, cyclophosphamide, cyclosporine and azathioprine are not approved treatments for IPF, and their efficacy is questionable and may increase mortality and exacerbation rates. Other treatments with anti-fibrotic action are currently being investigated. Pirfenidone has been the first product to receive EU and US approval as a treatment for mild to moderate IPF, because in these cases it significantly reduces the decline of lung function. Pirfenidone has antifibrotic and anti-inflammatory activity with a modest treatment effect.

Nintedanib, a tyrosine kinase inhibitor has been recently approved in EU and in USA for the treatment of patients with IPF. Nintedanib has shown to have a clinical benefit on slowing of deterioration in lung capacity with evidence of reduction of the rate of decline in lung function as indicated by absolute volume FVC.

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Finally oxygen therapy and non pharmacological treatment, such as pulmonary rehabilitation are usually recommended.

Dyspnea and cough are hallmark symptoms of IPF, and both appear to have important effects not only on quality of life (QoL) but also on survival [15]. IPF patients have unpredictable acute exacerbations, which could occur even with mild physiological impairment. At least half of hospitalizations are thought to be due to acute exacerbations of IPF [16]. Acute exacerbations of IPF are defined as an unexplained worsening or development of dyspnea. Their yearly incidence is between 10 and 15% of all patients. The prognosis of exacerbations is poor, with mortality ranging from 78% to 96% [22]. Other causes of exacerbations such as pulmonary embolism, congestive heart failure, pneumothorax, or infection need to be excluded.

Moreover, IPF patients experience depressive symptoms, which are correlated to QoL impairment and fatigue. QoL is further worsened as daily activities become restricted and patients grow increasingly oxygen dependent, debilitated, and dependent on others [15]. Not only prevalence of IPF is higher in men and in the older age groups, but also burden of disease [14]. In fact, higher increase in hospital admissions was found in men and older age groups by Navaratnam and colleagues [14]. They also estimated that the financial burden from IPF inpatient care alone in England is currently £16 million and will be almost £20 million by 2020.

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7. RESEARCH QUESTION AND OBJECTIVES

Long-term data on the natural course of IPF in Italy are scarce. Further, there is limited information on IPF in terms of patient characteristics and disease management. The purpose of the present study is to evaluate the characteristics, management and clinical course of patients with IPF as treated under real-world in Italian Pulmonary Centres, in terms of symptoms, lung function and exercise tolerance during 12 months of observation.

In particular, the study aims to provide information on disease characteristics and treatment modalities (at enrollment) and on disease progression, HRQoL and health care sector-related costs according to the Italian National Health Service (INHS) point of view (during 12 months of observation).

7.1 OBJECTIVES

Primary objective

1. In a sample of IPF diagnosed patients to describe the clinical course during 12 months of observation, in terms of:
   - symptoms
   - lung function (VC, FVC, FEV1, TLC, DLCO, pO2, pCO2; SaO2, PaO2 and PaCO2 at rest)
   - exercise tolerance (6-minute walk distance test)

Secondary objective

1. Description of characteristics of IPF patients at enrollment in terms of:
   - key (socio-) demographic data
   - IPF risk factors, comorbidities
   - IPF disease severity and manifestation (including lung function, cardiopulmonary exercise testing and/or exercise capacity if available, laboratory values)
   - Methods used for IPF diagnosis
   - IPF treatment modalities (detailed information on prescribed drugs and dose; non-pharmacological treatment; lung transplantation)
2. To describe the frequency of exacerbations during 12 months of observation.
3. To describe HRQoL variation, measured with SGRQ, EuroQol (EQ) 5-dimension 5-level (EQ-5D-5L) descriptive system and EQ VAS, during 12 months of observation.
4. To describe health care sector-related costs from diagnosis up to the end of 12-month follow-up according to the Italian National Health Service (INHS) point of view.

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8. RESEARCH METHODS

8.1 STUDY DESIGN

This is an observational, multicenter prospective cohort study based on newly collected data, involving 20 Italian Pulmonary Centers highly experienced in the disease management of IPF.
The enrolment period will last 18 months. During this period, about 200 consecutive patients will be included in agreement with the inclusion/exclusion criteria. Patients will be followed up for 1 year, with 3 intermediate evaluations after 3 (+/-1), 6 (+/-1) and 9 (+/-1) months from baseline (such visits are referred as being the current clinical practice in Italy for IPF patients management).
No treatment will be administered to the patients on the protocol basis, since this is an observational study and the assessment and treatment of the enrolled patients is based only on the investigators' clinical routine practice.

8.2 SETTING

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site irrespective of whether they have been treated or not.

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. Any administrative reasons that could significantly affect continuation of the study according to signed site contract
3. Violation of GCP, the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduction 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).

All patients referring to pulmonary centers will be consecutively enrolled according to the following criteria:

Inclusion Criteria

1. Patients aged>=40 years
2. Written informed consent to both participation in the study and privacy

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3. Physician diagnosed IPF during the last 3 months based upon recent ATS/ERS/JRS/ALAT guidelines 2011 (see Tables A1-A2 for HRCT and histology criteria):
    - 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 HRCT and surgical lung biopsy (see Tables A1-A2 for details) if available.
4. Patient with further follow-up possible with enrolling investigator during planned study period
5. Patients capable of discernment and able to read or write in Italian language.

Exclusion Criteria

1. Inclusion in clinical trials or other IPF/ILD registries
2. Lung transplantation expected within the next 6 months.
3. Pregnancy or breast feeding

Study-exit Criteria

1. Inclusion in clinical trials
2. Consent withdrawal (from patient or legally accepted representative)
3. The patient was erroneously included in the study
4. Pregnancy or breast feeding
5. Any other reason as agreed to by the investigator and the BITSPA clinical monitor

8.3 VARIABLES

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. The treating physician is asked to complete if possible at every patient visit the appropriate CRF.

Primary endpoints will be: symptoms, lung function (VC, FVC, FEV1, TLC, DLCO, pO2, pCO2; SaO2, PaO2 and PaCO2 at rest), exercise tolerance (6-minute walked distance test) both at baseline and at follow-up visits.
Secondary endpoints will be: (socio-) demographic data, IPF risk factors, comorbidities, IPF disease severity and manifestation (including lung function, cardiopulmonary exercise testing and/or exercise capacity if available, laboratory values), methods used for IPF diagnosis, IPF treatment modalities (prescribed drugs and dose; non-pharmacological treatment; lung transplantation); exacerbations SGRQ and EuroQol (EQ) 5-dimension 5-level (EQ-5D-5L). Finally health care resources will be collected

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Below is the recommended assessment schedule that most likely mirrors the patterns of routine clinical care of most patients.

Study Visits	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
	Baseline	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**	**Follow-up 4**
Months	**0**	**3 (+/-1)**	**6 (+/- 1)**	**9 (+/- 1)**	**12 (+/- 1)**
Eligibility criteria Inclusion and exclusion criteria, Informed consent and privacy form	X				
Baseline information (Socio-)demographic variables: age, gender, race, body mass index, geographic location, educational degree, marital status, housing situation and employment status	X				
Potential IPF risk factors Cigarette smoking (including pack/years), environmental exposure, drug exposure, family history, other	X	X	X	X	X
Comorbidities Atherothrombotic disease including coronary heart disease, previous myocardial infarction, cerebrovascular disease, peripheral arterial disease, gastroesophageal reflux disease, pulmonary hypertension, emphysema, lung cancer, renal insufficiency	X	X	X	X	X
Baseline information on IPF First symptoms; date of first diagnosis; if performed, dates and results of HRCT, surgical lung biopsy, bronchoalveolar lavage.	X				
IPF Symptoms Cough, Fatigue, Dizziness, Chest pain, Clubbing, Bibasilar crackles.	X	X	X	X	X
Functional assessment Lung function test (VC, FVC, FVC % predicted, FEV1, TLC, DLCO, DLCO % predicted, pO2, pCO2; SaO2, PaO2 and PaCO2 at rest); 6-minute walk distance (if performed)	X	X	X	X	X
Exacerbations Onset and end date Description of management (if available)	X	X	X	X	X
Pharmacological treatments related to both IPF and adverse events (drug, dosage regimen, start / end date or ongoing): Steroids, anticoagulants, immunomodulators (azathioprine, cyclophosphamide, MMF, etc), N-	X	X	X	X	X

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Study Visits	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
	Baseline	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**	**Follow-up 4**
Months	**0**	**3 (+/-1)**	**6 (+/- 1)**	**9 (+/- 1)**	**12 (+/- 1)**
Acetylcysteine, Pirfenidone, Nintedanib					
Presence on listing for lung transplantation (yes/no)	X	X	X	X	X
Non Pharmacological treatment - Pulmonary rehabilitation; - Long-Term Oxygen Therapy (liquid and/or concentrate).	X	X	X	X	X
Health-care resource consumption related to both IPF and IPF-related adverse events: hospitalization (inward and day-hospital), emergency room access, specialist visits, General Practitioner visits, laboratory tests or examinations, imaging sessions, pharmacological and non-pharmacological treatments	X	X	X	X	X
Patient Reported Outcomes Questionnaires/scales					
HRQoL EQ-5D-5L descriptive system and EQ VAS; Saint George Respiratory Questionnaire (SGRQ)	X		X		X
Survival Status		X	X	X	X
Adverse Events and Adverse Drug Reactions description, onset and resolution date, relation with drugs, severity, seriousness.		X	X	X	X
Clinical events CNS infarction; myocardial infarction; other arterial thromboembolic events; deep vein thrombosis; hemorrhage; gastrointestinal perforation; pulmonary hypertension)		X	X	X	X

Visit 2 (3+/-1 month), Visit 3 (6+/-1 month) and Visit 4 (9+/-1 month) are referred as being the current clinical practice in Italy for IPF patients management.

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Data will be collected at baseline, 3, 6, 9 and 12-month follow up visits for routine clinical practice and the following questionnaire and scales will be administered to patients: Modified Medical Research Council Dyspnea Scale (MMRC); Morisky medication Adherence Scale 4 items (MMAS-4); EuroQoL-5D 5L; Hospital Anxiety and Depression Scale (HADS); Saint George Respiratory Questionnaire (SGRQ) (see Variables section for details).
The following procedures will be applied at each study visit according to routine clinical practice:

- Lung function test (VC, FVC, FEV1, TLC; DLCO; pO2, pCO2; SaO2, PaO2 and PaCO2 at rest);
- 6-minute walked distance test.

Acute exacerbation of IPF (AE-IPF) will be defined as a sudden acceleration of the disease or an idiopathic acute injury superimposed on diseased lung that leads to a significant decline in lung function. It will be evaluated according to clinical judgement.

EuroQoL-5D

The quality of life will be evaluated by the EQ-5D-5L a standardize measure of health status developed EuroQol Group to provide a simple generic measure of health status for clinical and economic evaluation [38, 48]. EQ-5D-5L is filled in by patients, it's easy from a cognitive point of view, since it takes only few minuts for filling.
EQ-5D-5L consists of 2 sections: "EQ-5D descriptive system" and EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression.
The EQ VAS indicate the health status self-assessed by the patient on a visual analogue scale from 0 to 100, where 100 is the "best imaginable health state" and 0 the "worst imaginable health state". It can be used as a quantitative measure of health as judged by respondents.
The questionnaire will be completed by patients at enrolment, 6-, and 12-month follow up visits.

St. George's Respiratory Questionnaire (SGRQ)

Health Related Quality of Life will be assessed by the St. George's Respiratory Questionnaire, developed to measure health in chronic airflow limitation. It is a disease-specific instrument designed to measure health impairment in terms of impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease [39] .

It consists of 2 parts and 3 different components as follows:
Part 1 (Symptoms component): addresses the frequency of respiratory symptoms and its purpose is to assess the patient's perception of his/her recent respiratory problems.

Part 2: addresses the patient's current state.

- Activities component measures disturbances to daily physical activity;

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- Impact component covers a range of disturbances of psycho-social function.

Three component scores are calculated: symptoms, activity and impacts on daily life. Moreover a total score will be calculated, with lower scores corresponding to better health [40, 41].
It has good discriminative and evaluative properties; it was developed and validated in both asthma and COPD, although it has also been validated for use in bronchiectasis and has been applied to patients with sarcoidosis. It takes 8-15 minutes to complete and it can be easily self-administered to patients. The Italian version of this questionnaire is available.
The questionnaire will be completed by patients at enrolment, 6- and 12-month follow up visits.

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8.4 DATA SOURCES

Source data will be medical records usually collected during routine clinical practice other than study-specific questionnaires.
Collected variables are defined based on study objectives and according to the observational nature of the study. They consist in data routinely collected in clinical practice, so they are expected to be available in medical charts.
The study data will be collected by means of remote data capture using an electronic case report form (eCRF). Investigators will be provided a user-friendly paper form which is intended as a supportive tool for data collection and will be filled in according to each site specific need (it will not be considered as a source data).
Patient-reported outcomes, i.e. scales and questionnaires, will be collected on paper and they will constitute source data.

8.5 STUDY SIZE

The sample size was determined on the basis of feasibility criteria. In fact, according to the volume of patients managed by the centers involved in this study, inclusion of 200 subjects (10 patients/center) with the characteristics defined at Inclusion/Exclusion criteria paragraphs is deemed reasonable for enrolment period (18 months).
An evaluation of the possible achievable precision of the estimates was performed considering the primary objective of the study and literature data, when available.
The primary objective of the study is to describe the clinical course during 12 months of observation, in terms of symptoms, lung function and exercise tolerance. Assuming a drop-out rate ranging from of 20% to 40%, the total number of evaluable patients at 12-month follow-up visit is expected to range between 120 and 160 subjects. Drop-out rate was hypothesized by considering mortality rate in IPF patients and natural drop-out from studies. Literature data about the clinical course of outcomes of interest in IPF patients in a real-life context are scanty. Nishiyama et al. [35] conducted a study on 93 IPF patients and assessed the pulmonary function. The mean (±SD) of FVC, FEV1, DLCO were 2.37 (±0.73) L, 1.93 (±0.57) L and 9.19 (±3.92) mL*min-1*mmHg-1 respectively. According to the data of a recently completed trial on patients with IPF by Swigris et al [37], the mean (±SD) baseline

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6-min walked distance was 372.9 (±82.63) meters. Regarding the most common IPF symptoms, clubbing, dyspnea (evaluated by means of a mMRC score ≥2), crackles and cough frequencies are 43%, 44%, 67% and 73% respectively [34, 35].

Table 1 shows the two-sided 95% confidence interval (CI) for expected frequency of IPF symptoms for a sample size n=120 and 160, using the large sample normal approximation [36].

	Expected frequency	95% CI	
IPF symptoms			
n=120			
Clubbing	43%	34.1%	51.9%
Dyspnea (mMRC score ≥2)	44%	35.1%	52.9%
Crackles	67%	58.6%	75.4%
Cough	73%	65.1%	80.9%
n=160			
Clubbing	43%	35.3%	50.7%
Dyspnea (mMRC score ≥2)	44%	36.3%	51.7%
Crackles	67%	59.7%	74.3%
Cough	73%	66.1%	79.9%

Table 1 *two-sided 95% CI of expected frequency for IPF symptoms with sample sizes n=120 and 160. Cells are gray when the relative error - calculated as the ratio between 95% CI half-width and expected frequency - is lower than 30%.*

Table 2 shows the two-sided 95% CI for expected mean of FVC, FEV1, DLCO and 6-min walked distance for sample sizes of n=120 (drop out=40%) and n=160 (drop out=20%), assuming the SD reported in the table and the confidence interval is based on the large sample z statistic [36]. IPF is a degenerative disease, therefore it is expected a worsening of symptoms, lung function and exercise tolerance. However, a conservative evaluation was performed by taking into account the two-sided 95% confidence interval.

	Expected mean	SD	95% CI	
n=120 (drop out=40%)				
FVC (L)	2.37	0.73	2.24	2.50
FEV1 (L)	1.93	0.57	1.83	2.03
DLCO (mL*min-1*mmHg-1)	9.19	3.92	8.49	9.89
6-min walked distance (m)	372.9	82.63	358.12	387.68
n=160 (drop out=20%)				
FVC (L)	2.37	0.73	2.26	2.48
FEV1 (L)	1.93	0.57	1.84	2.02
DLCO (mL*min-1*mmHg-1)	9.19	3.92	8.58	9.80
6-min walked distance (m)	372.9	82.63	360. 1	385.70

Table 2 *two-sided 95% CI of expected FVC, FEV1, DLCO and 6-min walked distance mean with sample sizes n=120 and 160. Cells are gray when the relative error - calculated as the ratio between 95% CI half-width and expected mean - is lower than 30%.*

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8.6 DATA MANAGEMENT

The CROs in charge of the study is
The data entered into the eCRFs by investigational staff will be reviewed for completeness and accuracy and the site personnel will be instructed to data entry data into the eCRFs and to make any required corrections or additions during the phone training. The eCRF will be provided by online edit checks. The Data Manager will perform the cleaning session by running post-entry checks by means of validation programs and data listings specific for the study. During this process, if clarifications are needed, the Data Manager will raise queries by means of data query forms through the application. Designated investigator site staff is required to respond to the query and make the correction to the database.
Patients violating inclusion or exclusion criteria will not be considered for analyses. A description of reasons of violation will be provided anyway. After these actions have been completed and the database has been declared to be completed and accurate, it will be locked and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Medical Adviser, the Study Statistician and the Data Manager. Only authorized and well-documented updates to the study data will be possible after database lock.
Each participating site will maintain appropriate medical and research records for this study, in compliance with GPP and regulatory and institutional requirements for the protection of confidentiality of subjects.
Patient initials or names will not be recorded in the database: patients will be associated to a unique identifier, assigned as a progressive number within each site. Due to the observational nature of the study no independent review of the data will be performed.
Data access rules, as well as data transfer to Sponsor, will be detailed in the Data Management Plan.

8.7 DATA ANALYSIS

The statistical analysis will be performed on all evaluable patients who enter the study and meet the inclusion criteria. Patients with missing values will not be excluded from the analysis, their data will not be replaced; frequency of missing data will be given for all analyzed variables.
Descriptive analysis will be composed of means, medians, quantiles, proportions (with their respective 95% confidence intervals, CI) and contingency tables according to the nature of the variables. As a dispersion measurement the standard deviation and the interquartile range will be calculated. All events during follow-up will be described as incidence rates with 95% CI.
Statistical analysis will be performed using the SAS software.
The study objectives will be evaluated as follows:

Primary objective

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To describe the clinical course of IPF during 12 months of observation

At each follow up visit the frequency of IPF symptoms (cough, fatigue, dizziness, chest pain, clubbing, bibasilar crackles) will be provided and the variation between visits will be described too mostly in terms of incident and worsening symptoms. Moreover, the score of the Modified Medical Research Council Dyspnea Scale for the evaluation of dyspnea at each follow up visit will be calculated together with the variation since baseline and between follow up visits.

The following outcomes will be also considered during the 12-month observation: lung function parameters (like VC, FVC, FEV1, TLC, DLCO, pO2, pCO2; SaO2, PaO2 and PaCO2 at rest) and patient's exercise capacity (evaluated by means of 6-minute walked distance test, if available). The outcomes will be described at each follow up by means of descriptive statistics and the variation between visits will be provided too.

Secondary objectives

#1 Description of IPF patients at enrollment (socio-demographic data, IPF risk factors, comorbidities, disease severity and manifestation, methods for diagnosis, treatment modalities)

IPF patients enrolled at baseline will be described in terms of socio-demographic variables (e.g. age, gender, race, body mass index, educational degree, and employment status) and potential IPF risk factors (such as smoking habits, environmental exposure, drug exposure, other factors).

The absolute and relative frequency distributions of patients (N, %) according to ongoing comorbidities (such as gastroesophageal reflux disease, pulmonary hypertension, emphysema, lung cancer, coronary heart disease, depression) will be also provided at baseline.

Treatment modalities will be described at each visit by means of frequency distribution of patients according to ongoing therapies for IPF; pharmacological (such as steroids, anticoagulants, immunomodulators, N-acetylcysteine, pirfenidone, etc..) and non-pharmacological (such as long term oxygen and pulmonary rehabilitation) therapies will be considered and described in terms of drug, dosage regimen and duration/number of sessions (including start and stop dates). The frequency of patients on listing for lung transplantation at baseline will be also provided.

#2 To describe the frequency of exacerbations during 12 months of observation

The proportion of patients with at least one exacerbation after 12 months of observation will be computed as the ratio between the number of patients with one or more episodes of

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exacerbation occurred during 12 months of follow up over the total number of evaluable patients. Patients who drop-out without having exacerbations before the end of the study, will be considered in the denominator of the proportion of interest. The median number of episodes of exacerbation per patient will be provided. Finally time to first exacerbation will be analyzed by Kaplan-Meier curves.

#3 To describe the HRQoL variation during 12 months of observation

The digits for EQ-5D-5L 5 dimensions can be combined in a 5-digit number describing the respondent's health state. An appropriate algorithm will be used to summarize data in an overall score ranging from -1 (worse-than-death health status) to 1 (best health status) [38, 48].
The descriptive statistics will be produced for EQ-5D-5L descriptive system index and VAS . Moreover, the difference of scores between baseline and available follow up visits will be calculated too.
Similarly, the descriptive statistics of St. Georges Respiratory Questionnaire scores (symptoms, activity and impacts and total score) will be calculated. The St. Georges Respiratory Questionnaire is a self-completed questionnaire for measuring impaired health in patients with chronic lung disease. The descriptive statistics of weighted single scores (symptoms, activity and impacts and total score) will be calculated. Graphs of mean HRQoL scores according to visits will also be provided to show the trend of variation, if any.

#4 To describe health care sector-related costs during 12 months of observation

In order to describe health care sector-related costs at diagnosis and from diagnosis up to the end of 12-month follow-up according to the INHS point of view, a two steps approach will be followed: (i) first of all the resource consumption since diagnosis will be collected or estimated and then (ii) a monetary value will be assigned to the collected or estimated resource consumption.
(i) Health care resource consumption exclusively related to both IPF and IPF-related adverse events will be computed during observational period in terms of pharmacological and non-pharmacological treatments, number of (inward and day-hospital) hospitalizations, number of emergency room visits, number of General Practitioner visits, laboratory tests or examinations (spirometry, BAL, saturation), number of imaging sessions. Health care resources consumed during a three-month span of time between date of diagnosis and inclusion in the study will be retrospectively collected via an ad hoc section of the case report form (CRF) and/or estimated.
(ii) In order to estimate the economic impact on health care sector-related costs of the above mentioned health services (hospital admissions, visits, treatments, examinations) consumption, a monetary value to each event recorded will be assigned, as defined by the Italian Ministry of Health through the tariff in force for outpatient setting [28]. The cost of hospitalization will be valued according to the most recent available diagnosis-related group (DRG) tariffs; finally pharmacological treatments will be costed at consumer price.

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All costs will be expressed in €. A monthly (or yearly) cost will be provided by taking into account patients according to duration of observation and parametrizing each patient to the 1-year observation period.

Cost of Illness (COI) will be analyzed via descriptive statistics (mean; standard deviation; median; minimum and maximum).
Non-parametric bootstrap method will be applied to COI data for calculating 95% confidence intervals.

8.8 QUALITY CONTROL

The Quality control will be managed in accordance with procedures as agreed with BITSPA.

8.8.1 STUDY MONITORING

On site and remote monitoring will be performed by who has been designated by BITSPA.

It is understood that the monitor(s) will contact and/or visit the Investigator/centre before the study start up, regularly throughout the study and after the study data collection will have been completed, and that they will be permitted to inspect the various study records: eCRFs, filled questionnaire, Investigator study file and source data (source data is any data that is recorded elsewhere to the eCRFs), provided that subject confidentiality is respected.

The purposes of these visits/phone contacts are:

- to assess the progress of the study;
- to review compliance with the study protocol;
- to discuss any emerging issue;
- to check the eCRFs for accuracy and completeness;
- to validate the contents of the eCRFs against the source documents (only by on side visits).

Prior to each on site monitoring visit, the Investigator or staff will record all data generated since the last visit on the eCRFs. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.

During each remote monitoring contact, the Investigator or staff will will be expected to be available for the phone call to answer questions and to provide any missing information.

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8.8.2 GUIDELINES FOR EPIDEMIOLOGICAL STUDIES

The guidelines for Good Pharmacoepidemiology Practices (GPP) in non-interventional studies as well as recommendations for non-interventional study and principles of epidemiology studies will be respected [47]. This study is not in the scope of Good Clinical Practice (GCP) studies, but for several applicable aspects it will be managed according to it.

8.8.3 CONFIDENTIALITY OF STUDY DOCUMENTS AND SUBJECT RECORDS

All study documents are provided by the Sponsor to the Investigator and his/her appointed staff in confidence. None of this material may be disclosed to any party not directly involved in the study without written permission from BITSPA.

The Investigator must assure that the subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject's study numbers, names and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from BITSPA.

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Only the subject number will be recorded in the case report form. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigators will maintain a list to enable subjects' records to be identified. However, if the results of the study are published, the subject's identity will remain confidential.

Personal data - including sensitive data - collected during the execution of the activities will be processed in accordance with the local laws on data protection.

8.8.4 INVESTIGATOR'S FILES / RETENTION OF DOCUMENTS

The Investigator must maintain adequate and accurate records to enable the conduct of this cohort study and the study data to be subsequently verified. These documents should be classified into two different separate categories (1) Investigator's Study File, and (2) subject clinical source documents.

The Investigator's Study File will contain the observational protocol study/amendments, EC/IRB approval with correspondence, sample informed consent, staff curriculum vitae and authorization forms and other appropriate documents/correspondence etc.

Subject clinical source documents would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, pathology and special assessment reports, signed informed consent and privacy forms, consultant letters and subject screening and enrollment logs. The Investigator must keep these two categories of documents on file according to local regulations after completion or discontinuation of the

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study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, BITSPA must be notified in advance.

8.8.5 LIMITATIONS OF THE RESEARCH METHODS

This is a descriptive epidemiological study which puts patients under observation for one year prospectively. However information, selection and/or recall bias have to be taken into account, as in all epidemiological studies.
Investigators could select patients in order to enroll those ones who most probably will be followed up (selection bias). In order to limit this bias, monitoring visits could be randomly performed in sites to verify whether enrolment was performed consecutively.
Recall bias could mostly affect healthcare resources consumption: this is the reason why it will be evaluated during prospective phase on a regular basis. The information are usually recorded in medical charts or there are questionnaires filled in during visit: this also should limit bias of information.

As regards confounding, the aim of the study is descriptive, i.e. no causality nor associations to treatments will be evaluated. It has to be kept in mind that the study regards a relatively rare, fast progressing disease, rare outcomes and a very heterogeneous patient population.

As far as generalizability of results, the study aims to provide information on IPF patients enrolled in the study; it does not mean to be generalized to all Italian IPF patients because sites are selected. In order to avoid patient selection during recruitment, sampling is based on consecutive enrolment.

In order to validate the CRF content a qualitative pre-test will be performed, by simulating data capture during study conduction.

As far as recognizing IPF in clinical practice can be challenging as symptoms often appear similar to those of more common diseases, such asthma, chronic obstructive pulmonary disease (COPD) and congestive heart failure. If IPF is suspected, diagnosis can be challenging but a multidisciplinary approach involving a pulmonologist, radiologist and pathologist expert in interstitial lung disease has been shown to improve the accuracy of IPF diagnosis. Therefore in order to maximize exposure measurement validity, all patients with diagnosis of IPF in the last 3 months will be enrolled. Diagnosis will be evaluated by clinical judgement.

Finally, target sample size is considered to be achievable during the enrolment period on the basis of preliminary feasibility considerations. Anyway, due to study design and inclusion

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criteria the number of enrolled patients is expected to be consistent with the total number of treated patients.

8.9 OTHER ASPECTS

8.9.1 INFORMED CONSENT, DATA PROTECTION, STUDY RECORDS

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 Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BITSPA Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.
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.

8.9.2 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.
Prior to patient participation in the study, written informed consent must be obtained from each patient according to ICH GCP and to the regulatory and legal requirements of Italy. 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 authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.9.3 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance

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auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with GPP.
The Investigators and Institution must permit study-related monitoring, audits, IRBs/IECs review or regulatory inspection, providing direct access to source data/documents.

8.9.4 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture.

8.9.5 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

8.9.6 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. FDA). The Clinical Research Associate (CRA) / on site monitor 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

8.9.7 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.

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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.

8.9.8 COMPLETION OF STUDY

The IRB/IEC/competent authority in Italy will be notified about the end of the study (date of termination of observational study, last patient patient out date, number of patients observed) or early termination of the observation.

8.9.9 PROTOCOL VIOLATIONS

Not applicable

8.9.10 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

Not applicable

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9. PROTECTION OF HUMAN SUBJECTS

This study was designed and shall be implemented and reported in accordance with the Guide on Methodological Standards in Pharmacoepidemiology (Revision 3, July 2014) of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, with the ethical principles laid down in the Declaration of Helsinki and with the laws and regulations of Italy in which the research is carried out, whichever affords the greater protection of the individual.

The study will be notified to the Health Authority according to the legal requirements in Italy as unique participating country.

Subjects selection will not start before the approval of the EC/IRB and notification of the study to the Health Authority. This study does not include treatments or diagnostic examinations other than those prescribed in the ordinary clinical practice, therefore no insurance agreements are applicable.

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10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

10.1 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 unfavourable 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 authorization 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 hospitalization,
- 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 judgement 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)

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The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

10.2 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 authorization. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BITSPA drug. 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 for the BITSPA product administered for the disease in scope of the study:

- all ADRs (serious and non-serious),
- all AEs with fatal outcome ,
- all pregnancies

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

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- 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 the BITSPA drug taken for the disease in scope of the study, 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

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The following must be reported by the investigator on the NIS AE form (or pregnancy monitoring form if applicable) from signing the informed consent onwards until the end of the study for the BITSPA product administered for the disease in scope of the study:

Type of Report	Timeline
All **SADRs**	immediately within 24 hours
All **AEs with fatal outcome**	immediately within 24 hours
All **non-serious ADRs**	7 calendar days
All **pregnancies**	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.

Reporting of related Adverse Events associated with any other BITSPA drug

The investigator is encouraged to report all adverse events related to any BITSPA drug other than the BITSPA drug taken for the disease in scope of the study 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.

10.3 REPORTING TO HEATH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements. Also the investigator is encouraged to report all adverse event related to any drug to LHA according to local regulatory requirements.

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11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The end of the data collection (including the follow-up period) for this observational study is expected within 2018, depending on the enrolment period necessary to collect data from at least two hundred patients.
The final study report should be submitted as soon as possible within 12 months of the end of data collection.
The final study report, including the statistical and clinical evaluations, shall be prepared and sent to the Advisory Board, for agreement and signature.
At the end of the study a summary of the final study report will be provided to all ECs/IRBs, to the Italian Competent Authority, only if requested, and to Investigators.

BITSPA is entitled to publish and/or present any results of this study at scientific meetings; BITSPA furthermore reserves the right to use such data for industrial purposes.
Investigators will inform the Advisory Board and BITSPA before using the results of the study for publication or presentation, and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual study sites shall not be published separately before main study paper based on global data collected will be published.

11.1 OPERATIVE MANAGEMENT OF MEDICAL WRITING ASPECTS

The results of this study will be published or presented at scientific meetings. Participant Investigator agrees to submit all manuscripts or abstracts to BITSPA prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.
In accordance with standard editorial and ethical practice, BITSPA will generally support publication of multicenter studies only in their entirety and not as individual center data. In this case, the Study Advisory Board will be designated.
The investigator has to provide the sponsor all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials, is the sole responsibility of the sponsor.
Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Study Site Agreement, which has to be written consequently.

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BITSPA also adheres to any additional standards concerning authorship required by a specific journal or congress to which the publication is submitted. The responsible individuals at BISPA apply, at a minimum, the following criteria to determine who is named as an author on a publication:

- Substantial contributions to the concept and design, acquisition of data, or analysis and interpretation of data
- Drafting of the publication or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Authorship criteria and obligations apply equally to BITSPA employees and non-employees. Each listed author must have participated in the work enough to take public responsibility for appropriate portions of the content.
Individuals contributing to the publication but not meeting authorship criteria may be appropriately acknowledged in the publication.

11.2 GHOSTWRITING AND GUEST/GHOST AUTHORSHIP

Ghostwriting, guest authorship, and ghost authorship are strictly prohibited. The contribution of a writer, which, when performed under the direction of the author(s), is considered a form of specialized, technical assistance, is acknowledged in the earliest draft in which the writer is involved.

11.3 DETERMINING ORDER OF AUTHORSHIP

Author order is determined by mutual agreement at the earliest possible time, with due consideration to overall contributions to the study, to the publication, or to scientific knowledge of the subject matter.

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12.2 UNPUBLISHED REFERENCES

Not applicable.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	1	*26th June, 2015*	List of BITSPA allocated Team
2	2	*26th June, 2015*	List of all main Principal Investigators participant to the study
3	3	*26th June, 2015*	List of Advisory Board members
4	4	*26th June, 2015*	List of allocated Team
5	5	*26th June, 2015*	Assessment of IPF with HRCT or/and surgical lung biopsy
6	6	*26th June, 2015*	Approval/signature page

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ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

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

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

In question 9.5 of the Checklist, Revision 1:

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

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ANNEX 3. ADDITIONAL INFORMATION

None.