Boehringer Ingelheim

Non-interventional Study Protocol

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Title:	Observational Analysis on the Socio-economic Impact of IPF in Spain.
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Joint PASS:	No

Research question and objectives:	Primary Objective: - To compare the economic impact of Idiopathic Pulmonary Fibrosis (IPF) according to FVC % predicted level (FVC<50%, FVC 50-80%, FVC>80%), in adult patients through estimation of annual direct and indirect costs associated with the disease at one year. Secondary Objectives: - To estimate the QoL of the patients with IPF according to FVC % predicted level, through SGRQ and EQ-5D-5L questionnaires and the Barthel index. - To explore the determinants of costs and QoL in patients with IPF according to FVC % predicted level - To characterize acute IPF exacerbations over one year (frequency and cost) according to FVC % predicted level. - To estimate the impact of FVC deterioration, in cost and QoL of the patient. - To explore the impact of the disease on the patient's caregiver through Zarit Burden Interview questionnaire at 6 and 12 month.
Country of study:	Spain
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Marketing authorisation holder(s):	Boehringer Ingelheim International GmbH Binger Str. 173 D-55216 Ingelheim am Rhein Germany
MAH contact person:	Not applicable.
EU-QPPV:	Not applicable.
Signature of EU-QPPV:	Not applicable.
Date:	15 Jun 2017

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
BI	Boehringer Ingelheim
BMI	Body Mass Index
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DLCO	Diffusing capacity of the lung for carbon monoxide
eCRF	Electronic Case Report Form
EQ-5D-5L	EuroQoL five dimensions questionnaire 5L
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
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
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IPF	Idiopathic Pulmonary Fibrosis
IRB	Institutional Review Board
MAH	Marketing Authorisation Holder Activities
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
QoL	Quality of Life
SAE	Serious Adverse Event
SGRQ	St. George's Respiratory Questionnaire
UIP	usual interstitial pneumonia
6MWD	6 Minutes Walk Distance test

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Not applicable			
Name of active ingredient: Not applicable			
Protocol date: 15 Jun 2017	**Study number:** 1199-0296	**Version/Revision:** 1.0	**Version/Revision date:** Not applicable
Title of study:	Observational Analysis on the Socio-economic Impact of Idiopathic Pulmonary Fibrosis (IPF) in Spain.		
Rationale and background:	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, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP) (1). On the other hand, there is no evidence on the costs of patients with IPF in Spain based on actual clinical practice. The only study carried out in Spain is based on Delphi panels and concluded that the management of patients with IPF in Spain, especially patients with rapid disease progression, has a high economic impact on the NHS (2). Nevertheless the study did not provide any information on the burden of disease by level of severity or from the societal perspective. The cost associated with acute exacerbations represents nearly half of the total cost of managing patients with IPF (2). Therefore, considering that low forced vital capacity (FVC) has proven the most consistent risk factor for acute exacerbation of IPF (3) is expected that patients with low FVC (FVC < 50%) have higher cost. The overall burden associated with IPF patients in Spain remains unknown. It is of great interest to develop studies analyzing the Cost-of-illness to define the magnitude of the disease in monetary terms and thereby to prove what the real impact of the disease is on the Spanish society (4). On the other hand, the social impact of IPF is also unknown, so studies that analyze the social perspective[1], in addition to the economic perspective, are necessary. The management of IPF in Spain is complex (see the image below – IPF patient pathway in Spain). Patients are diagnosed in a hospital and then may initiate treatment (antifibrotic or not). If patients receive an antifibrotic drug, they have to collect this in the hospital pharmacy. The follow-up visits are in the hospital		

[1] The perspective of society is the broadest of all perspectives because it is the only one that considers the benefit to society as a whole. Theoretically, all direct and indirect costs are included in an economic evaluation performed from a societal perspective. Costs from this perspective include patient morbidity and mortality and the overall costs of giving and receiving medical care. An evaluation from this perspective also would include all the important consequences an individual could experience. In countries with nationalized medicine, society is the predominant perspective. (Waning, B., Montagne, M., & McCloskey, W. W. (2001). *Pharmacoepidemiology: Principles and practice*. New York: McGraw-Hill.)

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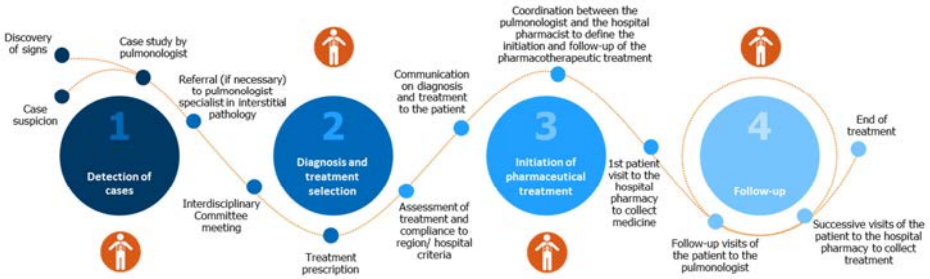
	(pulmonologist). Patients also go to the primary care physician regularly.  The present study aims at estimating the economic and -social impact of Idiopathic Pulmonary Fibrosis (IPF) in Spain.		

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Research question and objectives:	Primary Objective: - To compare the economic impact of Idiopathic Pulmonary Fibrosis (IPF) according to FVC % predicted level (FVC<50%, FVC 50-80%, FVC>80%), in adult patients through estimation of annual direct and indirect costs associated with the disease at in one year. Secondary Objectives: - To estimate the QoL of the patients with IPF according to FVC % predicted level, through SGRQ and EQ-5D-5L questionnaires and the Barthel Index at baseline. - To explore the determinants of costs and QoL in patients with IPF according to FVC % predicted level. - To characterize acute IPF exacerbations along one year (frequency and cost) according to FVC % predicted level at baseline. - To describe the variation of costs and QoL with IPF progression (according to the FVC deterioration). - To explore the impact of disease on the patient's caregiver through Zarit Burden Interview questionnaire at 6 and 12 month.		
Study design:	Non-interventional multicenter study based on newly collected data of Idiopathic Pulmonary Fibrosis patients followed-up for one year in secondary care settings (Pulmonology Services). IPF patients will be enrolled in a consecutive manner over a period of 6 month.		
Population:	Inclusion criteria: - Female and male patients ≥ 40 years of age. - Patients diagnosed with Idiopathic Pulmonary Fibrosis (IPF) according to last ATS/ERS/JRS/ALAT IPF guideline for diagnosis and management consensus (*1*). - Written informed consent prior to participation. Exclusion criteria: - Inability for the patient to understand or complete the written Informed Consent or patient questionnaires or to understand Spanish. - Current participation in any clinical trial. - Patients for whom further follow-up is not possible at the enrolling site.		
Variables:	- Sociodemographic variables: age, gender, employment, net incomes. - Anthropometric variables: weight, height and BMI. - Characteristics of IPF: date of IPF diagnosis, FVC (ml), FVC % predicted, FVC rate reduction during one year, DLCO, the Barthel index, 6MWD and		

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	concomitant diseases related to IPF. - Smoking status. - Work with animals (now or in the past) - IPF related resource use: primary and secondary care visits, outpatient visits, emergency visits (primary care and hospital), hospitalizations, ICU with and without intubation, outpatient tests and other examinations, use of transport, use of formal and informal caregiver, pharmacological and non-pharmacological treatments related to IPF, orthopedic material, formal social services, economic aid and structural adaptations. This data will be collected from the patient's medical records and by the patient through an interview during the visits and an individual patient's diary. - Days off work due to IPF - Sociodemographic variables for the caregiver (if applicable): age, gender, employment, and relationship with the patient. - IPF related days off work from patient's caregiver (if applicable) - QoL of the patients (SGRQ and EQ-5D-5L questionnaires) - QoL of the patients' caregiver (Zarit Burden Interview questionnaire) - Acute IPF exacerbations (An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality)[2] (5).
Data sources:	This non-interventional study will be based on both newly collected data and existing information. Data on patient QoL, caregiver burden, anthropometric variables, acute IPF exacerbations, use of resources, characteristics of IPF, will be collected from routine clinical care using medical records and patient's diary. Such medical records will also be used for sociodemographic and anthropometric variables, characteristics of IPF, smoking status, IPF related resource use and IPF days off work. Three visits per patient will be performed as per clinical practice (the closest visit to 6 months or 12 months after baseline). To be completed by the physician (newly data and existing information): - Patient demographics and medical data To be completed by the patient along the study (newly data): - Patient diary

[2] *Actue IPF exacerbation: An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality*

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	To be completed by the patient at inclusion visit , 6 month and 12 month (newly data): SGRQ and EQ-5D-5L To be completed by the caregiver at inclusion visit, 6 month and 12 month: - Zarit Burden Interview The direct costs over the 12 month follow-up period will be quantified by multiplying the recorded natural units of use of resources by the unit costs obtained by consulting Spanish databases or similar studies. The opportunity cost method will be used to calculate informal care costs. The indirect costs will be estimated by applying salary costs based on the latest data published by the Spanish Instituto Nacional de Estadística (INE) (*6*) from the salary structure survey, adjusted to age
Study size:	In view of the lack of Spanish studies that analyze the economic impact of Idiopathic Pulmonary Fibrosis (IPF) according to deterioration in the predicted forced vital capacity (FVC), and as this is a non-interventional study based on newly collected data, it was decided to observe all the patients with IPF that meet the inclusion/exclusion criteria during the inclusion period. Based on the investigation into the viability of recruitment, we expect to include 200 patients approximately. The primary objective of the study, if the sample size allow, is to compare the economic impact according to FVC levels at one year. This would mean opting for a balanced sample size for the three comparison groups. However, knowing the approximate patient prevalence according to predicted FVC (5-11% predicted FVC <50%, 51-73% predicted FVC 50-80%, and 22-38% predicted FVC >80%) (*7*) sponsor's internal data and the expert panel group (investigator coordinators) data) we expect to find: • 10-22 patients with predicted FVC <50%. • 102-143 patients with predicted FVC 50-80%. • 43-76 patients with predicted FVC >80%. Depending on the final distribution obtained in terms of number of patients for each comparison group and given the exploratory nature of this study, it is expected that comparisons between some groups will have a descriptive approach, although the expected comparison analyses will be carried out as stated in this protocol. Although the expected number of patients with predicted FVC <50% is small, it should at least provide first insights into the costs within this patient subgroup. In view of the lack of previous data on the cost of the disease according to the study's primary endpoint in Spain, this will be the first Spanish cost comparison study according to predicted FVC.

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Data analysis:	- A descriptive analysis of all variables collected will be performed. - For each patient, the annual direct costs (primary and secondary care visits, outpatient visits, emergency visits -primary care and hospital-, hospitalizations, ICU with and without intubation, outpatient tests and other examinations, pharmacological and non-pharmacological treatments, use of transport, formal caregiver, orthopedic material, formal social services, economic aid and structural adaptations), and indirect costs (days off work and informal caregiver) will be quantified. Direct costs will be quantified by multiplying the natural units of use registered for each resource by the unit costs consulted in Spanish databases (Oblikue eSalud database[3]) or similar studies (similar literature published). Indirect costs will be estimated by applying the wage costs from the latest data published by the National Statistics Institute survey of the salary structure. - Mean, standard deviation, % confidence interval of the mean, median and interquartile range will be calculated for the scores obtained with the SGRQ questionnaire collected and absolute and relative frequencies will be calculated for the scores obtained with the EQ-5D-5L questionnaire collected. - If sample size allows for it, bivariate and multivariate analysis will be performed in order to explore the variables impacting costs and QoL for each study subpopulation (FVC<50%, FVC 50-80%, FVC>80%). Taking into account that the final number of patients expected for the FVC <50% stratum could be small and the limitations that a multivariate analysis might have, an exploratory bivariate analysis could be performed for this group with relevant variables. The bivariate analysis will include all the sociodemographic and clinical variables collected. Parametric (t-test, ANOVA) and non-parametric (Mann-Whitney, Kruskal-Wallis) exploratory statistical tests will be performed. - Descriptive analyses will be carried out of the total number of acute IPF-related exacerbations as well as the use of resources and costs associated with the events according to the predicted FVC at the time of inclusion (FVC <50%, FVC 50-80%, FVC >80%). - Descriptive analyses will be carried out of direct and indirect costs and patient quality of life according to the change in FVC over one year (<10%, from -5% to -10%, and >-5%).		

[3] The eSalud platform is the access portal to the Spanish healthcare costs database set up by Oblikue Consulting. Source: Spanish Health Costs Database: eSalud [Internet]. Barcelona: Oblikue Consulting, S.L. 2007 [date of access]. Available from: http://www.oblikue.com/bddcostes/

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Milestones:	Planned start of data collection: October-2017 Planned end of data collection: May-2019 Planned final study report: September-2019		

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
IEC approval	July 2017
Start of data collection	October 2017
End of data collection	May 2019
Final report of study results	September 2019

7. RATIONALE AND BACKGROUND

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, and associated with the histopathologic and/or radiologic pattern of UIP (1). FVC is a reliable, valid, and responsive measure of disease status in patients with Idiopathic Pulmonary Fibrosis (8).

There are no large-scale studies of the incidence or prevalence of IPF on which to base formal estimates. Prevalence estimates for IPF have varied from 2 to 29 cases per 100,000 in the general population (9, 10, 11, 12, 13). 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). It is estimated that IPF affects about 7,500 people in Spain (14), however prevalence and incidence for IPF in Spain has not been studied and is uncertain.

On the other hand there is no evidence on the cost of patients with IPF in Spain based on actual clinical practice. The only study carried out in Spain is based on Delphi panels and concluded that the management of patients with IPF in Spain, especially patients with rapid disease progression, has a high economic impact on the NHS. In that study the parameter that varied the annual cost per patient the most was the resource use associated with acute exacerbations (2). Nevertheless the study did not provide any information on the burden of disease by level of severity or from the societal perspective, nor took into account pharmacological costs as pirfenidone had not been reimbursed and was only available through compassionate use when the analysis was performed.

The cost associated with acute exacerbations represents nearly half of the total cost of managing patients with IPF (2). Therefore, considering that low forced vital capacity (FVC) has proven the most consistent risk factor for acute exacerbation of IPF (3) is expected that patients with low FVC (FVC < 50%) have higher cost. Furthermore, the recent introduction of new antifibrotic agents (nintedanib, pirfenidone) changed the therapeutic strategy, so did the total cost of the disease.

The overall burden associated with IPF patients in Spain remains unknown. It is of great interest to develop studies analyzing the Cost-of-illness to define the magnitude of the disease in monetary terms and thereby to prove what the real impact of the disease is on the Spanish society (4). On the other hand, the social impact[4] (15) of IPF is also unknown, so studies that analyze the social perspective in addition to the economic one, are necessary.

The present study arises with the objective of estimating the economic and social impact of Idiopathic Pulmonary Fibrosis (IPF) in Spain.

[4] The perspective of society is the broadest of all perspectives because it is the only one that considers the benefit to society as a whole. Theoretically, all direct and indirect costs are included in an economic evaluation performed from a societal perspective. Costs from this perspective include patient morbidity and mortality and the overall costs of giving and receiving medical care. An evaluation from this perspective also would include all the important consequences an individual could experience. In countries with nationalized medicine, society is the predominant perspective.

8. RESEARCH QUESTION AND OBJECTIVES

This non-interventional study based on newly collected data will address the following questions.

Primary Objective:

- To compare the economic impact of Idiopathic Pulmonary Fibrosis (IPF) according to FVC % predicted level (FVC<50%, FVC 50-80%, FVC>80%), in adult patients through estimation of annual direct costs (primary and secondary care visits, outpatient visits, emergency visits -primary care and hospital-, hospitalizations,…), and indirect costs (days off work and informal caregiver) associated with the disease during one year

Secondary Objectives:

- To estimate the QoL of the patients with IPF according to FVC % predicted level, through SGRQ and EQ-5D-5L questionnaires and the Barthel Index at baseline.
- To explore the determinants of costs and QoL in patients with IPF according to FVC % predicted level.
- To characterize acute IPF exacerbations along one year (frequency and cost) according to FVC % predicted level at baseline.
- To describe the variation of costs and QoL with IPF progression (according to the FVC deterioration).
- To explore the impact of disease on the patient's caregiver through Zarit Burden Interview questionnaire at 6 and 12 month.

9. RESEARCH METHODS

9.1 STUDY DESIGN

Descriptive prospective non-interventional multicenter study based on newly collected data of Idiopathic Pulmonary Fibrosis patients followed-up for one year in secondary care settings (Pulmonology Services).

Idiopathic Pulmonary Fibrosis patients who attend to a routine follow-up visit and fulfil inclusion/exclusion criteria will consecutively enrolled by the investigator of each center. Once patients give their informed consent, the investigator will collect in the Case Report Form (CRF) specifically designed for the study, the corresponding sociodemographic, clinical data and healthcare and non-healthcare resource use registered in the medical records and provided by the patients. Also, patients will be invited to complete the study questionnaires in the inclusion visit (T0), approximately at their six month visit (T6) and twelve month visit (T12). Patients will also have a patient diary where collect data (see section 9.4) between follow-up visits along 12 month.

Three visits per patient will be performed as per clinical practice (the closest visit to 6 months or 12 months after baseline). The inclusion period of the study will be from Oct 2017 to April 2018 and the follow-up will be 12 months for each patient and until April 2018 for the last patient.

9.2 SETTING

9.2.1 Study sites

It is planned that data of approximately 200 patients from approximately 25 sites (secondary care sites – Pulmonology services where IPF is diagnosed and managed) in Spain will be collected. All Idiopathic Pulmonary Fibrosis patients who are diagnosed with IPF and attend to a routine visit during the inclusion period and fulfill inclusion/exclusion criteria and provide informed consent to participate will be included in the study.

Since the primary objective of the study is to compare the annual total cost per patient in Spain, it is necessary to ensure that study population is representative of the entire national territory. Therefore, patients will be consecutively recruited from centers in different geographical areas according to the distribution of the overall population in this area. Site selection will be performed in order to secure representativeness of the IPF population. It has been settled that each investigator has to include approximately 8 patients.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the Investigator Site File (ISF).

9.2.2 Study population

Patients can be included if all of the following criteria are met:

Inclusion criteria:

1. Female and male patients ≥ 40 years of age.
2. Patients diagnosed with Idiopathic Pulmonary Fibrosis (IPF) according to last ATS/ERS/JRS/ALAT IPF guideline for diagnosis and management consensus (*1*)
3. Written informed consent prior to participation.

Exclusion Criteria:

1. Inability for the patient to understand or complete the written Inform Consent or patients questionnaires or to understand Spanish.
2. Current participation in any clinical trial.
3. Patients for whom further follow-up is not possible at the enrolling site.

9.2.3 Study visits

The visit flow chart list all data collected and indicates with an "x", the visit when they are collected. All data collected must be supported in the patient's source documentation.

Visit flow chart and data collection parameters:

	T0 *Baseline Visit*	*T6* *6 month visit (+/- 2 month)*	*T12* *12 month visit (+/- 1 month)*
Patient Informed Consent	x		
Patient's informal caregiver Informed Consent (if applicable)	x	x	x
Inclusion / Exclusion Criteria	x		
Date of Birth (Age)	x		
Gender	x		
Employment status (employment and net incomes)	x	x	x
Anthropometric variables (weight, height and BMI)	x	x	x
Date of IPF diagnosis	x		
FVC (ml, %)	x	x	x
FVC % predicted [1]	x	x	x
FVC rate change by year	x		x
DLCO (mmol/min/kPa)	x	x	x
DLCO % predicted	x	x	x
The Barthel index	x	x	x

	T0 *Baseline Visit*	*T6* *6 month visit (+/- 2 month)*	*T12* *12 month visit (+/- 1 month)*
6MWD	x		x
Smoking status[2]	x	x	x
Environmental and occupational exposures[3]	x		
Drugs of abuse[4]	x		
Exposure to drugs associated with pulmonary fibrosis[5]	x		
Exposure to viral infection with potential association with IPF[6]	x		
Concomitant diseases related to IPF (lung transplantation included	x	x	x
pharmacological and non-pharmacological treatments related to IPF	x	x	x
Patient diary review	x	x	x
IPF related resource use: primary and secondary care visits, outpatient visits, emergency visits (primary care and hospital), hospitalizations, ICU with and without intubation, outpatient tests and other examinations, use of transport, use of formal and informal caregiver,		x	x
IPF related resource use: orthopedic material, formal social services, economic aid and structural adaptations.			x
Days off work due to IPF		x	x
Sociodemographic variables for the caregiver (if applicable): age, gender, employment and relationship with the patient.	x		
Work productivity from informal patient's caregiver (if applicable)		x	x
QoL of the patients (SGRQ and EQ-5D-5L questionnaires)	x	x	x
QoL of the informal patient's caregiver (Zarit Burden Interview). If applicable.	x	x	x
Acute IPF exacerbations[7]	x	x	x
Safety: Adverse Drug Reactions (serious and non-serious), fatal AE, pregnancy	x	x	x

[1] *Patient group (FVC<50%, FVC 50-80%, FVC>80%) will be automatically calculated within the eCRF based on available patient data* (16)*:*
Men: FVC % predicted (%)= 100 FVC/(0,0678 T – 0,0147 E – 6.0548)
Women: FVC % predicted (%)= 100 FVC /(0,0454 T – 0,0211 E – 2.8253)
(FVC is FVC in liters, T is height in cm and E is age in years)

[2] *Ex-smoker: subject who has not smoked for a period ≥ 6 months since the current date.*
To measure the amount a person has smoked over a long period of time we use pack-year. It is calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked. For example, 1 pack year is equal to smoking 1 pack per day for 1 year, or 2 packs per day for half a year, and so on:
Number of pack-years = (packs smoked per day) × (years as a smoker) or
Number of pack-years = (number of cigarettes smoked per day/20) × number of years smoked.
[3] *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*
[4] *Categorized: Alcohol consumption: Drinker/ex-drinker/non-drinker/unknown. Cocaine consumption: Never / Past / Current / Unknown. Other*
[5] *Any exposure ticked in this category (Yes/No/Unknown): Amiodarone, Bleomycine, Nitrofurantoine, Methotrexate. Gold salts*
[6] *Serum antibodies for (Positive/Negative/not available): Ebstein-Barr Virus, Hepatitis C virus - Other positive*
[7] *Actue IPF exacerbation: An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality*

Study visits have been schedule according to routine care in clinical practices.

9.2.4 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. Administrative reasons i.e. lack of recruitment.
3. Violation of the protocol, the contract, or applicable laws and regulations for non-interventional studies (including Good Epidemiological Practices (GEP), Good Clinical Practice (GCP)), which could disturb the appropriate conduct of the NIS.

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

A patient can be withdrawn from the study for the following reasons:

- A patient or legally accepted representative withdraws consent
- The patient was erroneously included in the registry
- Any other reason as agreed to by the Investigator and the BI Clinical Monitor

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

The Investigator should indicate the date, and reason/s for discontinuation and data should be entered on the Electronic Case Report Form (eCRF) of the next planned visit.

9.3 VARIABLES

9.3.1 Exposures

Not applicable as this is a non-drug related study.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

Main sociodemographic and clinical variables will be collected in order to describe population included in the study.

In order to compare the economic impact of Idiopathic Pulmonary Fibrosis (IPF) according to FVC % predicted level (FVC<50%, FVC 50-80%, FVC>80%) in adult patients through estimation of annual direct[5] and indirect costs[6] associated with the disease, the following outcomes will be collected in the eCRF:

- IPF related resource use along 12 months (visit T6 and/or visit T12): primary and secondary care visits (T6, T12), outpatient visits (T6, T12), emergency visits (primary care and hospital) (T6, T12), hospitalizations (T6, T12), ICU with and without intubation (T6, T12), outpatient tests and other examinations (T6, T12), use of transport (T6, T12), use of formal and informal caregiver (T6, T12), pharmacological and non-pharmacological treatments (except treatments administered in hospitalization) (T6, T12), orthopedic material (T12), formal social services (T12), economic aid and structural adaptations (T12).
- IPF related days off work along 12 months (visit T6 and visit T12)

9.3.2.2 Secondary outcomes

In order to estimate the QoL of patients with IPF according to predicted FVC% through the SGRQ and EQ-5D-5L questionnaires and the Barthel index.

- Health-related quality of life (QoL) will be investigated with the St George's Respiratory Questionnaire (SGRQ) and the EQ-5D-5L questionnaire. Quality of life will be assessed at visits T0, T6 and T12.

(See section 9.7.1)

In order to explore the determinants of costs and QoL in patients with IPF according to FVC % predicted level, the following variables will be collected in the CRF at visit T0 and T12:

- Sociodemographic variables: age, gender, employment, net incomes (T0).
- Anthropometric variables: weight, height and BMI (T0).
- Characteristics of IPF: date of IPF diagnosis (T0), FVC (ml) (T0, T6, T12), FVC % predicted (T0, T6 and T12), FVC rate change by year (T0 and T12), DLCO (T0, T6 and T12), the Barthel Index (T0, T6 and T12), 6MWD (T0 and T12), concomitant diseases

[5] Direct costs: cost incurred for medical products and services used for the prevention, detection, and treatment of a disease.
[6] Indirect costs: costs incurred from missing work which is loss of productivity

related to IPF (T0, T6 and T12), pharmacological and non-pharmacological treatments related to IPF (T0, T6 and T12).
- Smoking status (T0, T6 and T12).
- Work with animals (now or in the past) (T0)
- Use of formal and/or informal caregiver (T0, T6 and T12).

The number of exacerbation[7] (*5*) events observed during the study period will also be explored for the cost and QoL determinants.

In order to characterize acute IPF exacerbations (*5*) during one year according to FVC % predicted level at one year, the following variables will be collected in the eCRF along the study (12 months).
- Acute exacerbation related resource use: primary and secondary care visits, outpatient visits, emergency visits (primary care and hospital), hospitalizations, ICU with and without intubation, outpatient tests and other examinations, use of transport, use of formal and informal caregiver, pharmacological and non-pharmacological treatments (except treatments administered in hospitalization) , orthopedic material, formal social services, economic aid and structural adaptations.
- Acute exacerbation related days off work
- The direct costs will be quantified by multiplying the recorded natural units of use of resources by the unit costs.

In order to estimate the direct and indirect costs according to FVC deterioration the following variables will be collected in the eCRF along the study (T0, T6 and T12).
- FVC % predicted along the study (T0, T6 and T12)
  Men: FVC % predicted (%)= 100 FVC/(0,0678 T – 0,0147 E – 6.0548)
  Women: FVC % predicted (%)= 100 FVC /(0,0454 T – 0,0211 E – 2.8253)
  (FVC is FVC in liters, T is height in cm and E is age in years).
- The calculated variable will be stratified into the following subgroups: ≤-10%, from -10% to -5%, and >-5% (9).
- IPF related resource use (visit T6 and/or visit T12): primary and secondary care visits, outpatient visits, emergency visits (primary care and hospital), hospitalizations, ICU with and without intubation, outpatient tests and other examinations, use of transport, use of formal and informal caregiver, pharmacological and non-pharmacological treatments, orthopedic material, formal social services, economic aid and structural adaptations.
- IPF related days off work

In order to explore the impact of the disease on the patient's caregiver, the Zarit Burden Interview will be performed at visits T0, T6 and T12.

[7] Actue IPF exacerbation: An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality

9.3.3 Covariates

See Section 9.2.3

9.4 DATA SOURCES

This non-interventional study will be based on newly collected data. However, medical records collected through routine clinical care will be used to assess the inclusion/exclusion criteria of patients.

Such medical records will also be used for sociodemographic and anthropometric variables, characteristics of IPF, smoking status, IPF related resource use and IPF days off work.

Barthel Index will be used to score the ability of a patient to care for himself. It consists of 10 items, the values assigned to each item are based on time and amount of actual physical assistance required if a patient is unable to perform the activity. The final scores range from 0 and 100. Patient scoring 100 is continent, feeds himself, dresses himself, gets up out of bed and chairs, bathes himself, walks at least a block, and can ascend and descend stairs.
Spanish validated version will be used.

Patients will be asked to complete a patient diary along the study, to record IPF related resource used and days off work to avoid memory omissions. Investigator will reconcile data from patient diary and medical records and check incongruences with the patients during the visits. Reconciled data will be entered in the eCRF.

Patients will be also asked to complete at visit T0, T6 and T12 the SGRQ and EQ-5D-5L questionnaires.

The St. George's Respiratory Questionnaire (SGRQ) is a 50-item questionnaire developed to quantify the impact of the disease on the health and QoL perceived by patients with respiratory diseases. It consists of 50 items divided into 3 scales: symptoms (frequency and severity of respiratory symptoms), activity (activity limitations due to dyspnoea) and impact (psychological and social functioning disorders caused by the disease). The final scores range from 0 (fewest limitations) to 100 (most limitations). Spanish validated version will be used.

The EQ-5D-5L consists of a questionnaire and a visual analogue scale (EQ-VAS). The EQ-VAS is a self-rated health status using a VAS. The EQ-VAS records the subject's perceptions of their own current overall health. The self-assessment questionnaire is self-reported description of the subject's current health in 5 dimensions i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The subject is asked to grade their own current level of function in each dimension into one of five degrees of disability (no problems, slight problems, moderate problems, severe problems, and extreme problems). This decision results in a 1-digit number expressing the level selected for that dimension. The digits for 5 dimensions can be combined in a 5-digit number describing the respondent's health state. Spanish validated version will be used.

Caregivers who have signed the specific written informed consent form will be asked to complete the Zarit Burden Interview. It is a self-report measure. The revised version contains

22 items. Each item on the interview is a statement which the caregiver is asked to endorse using a 5-point scale. Response options, in the Spanish version, range from 0 (Never) to 4 (Nearly Always). The final scores range from 0 and 88: Little or no burden (≤ 421), mild to moderate burden (22-40), moderate to severe burden (41-60) and severe burden (≥ 61).

9.5 STUDY SIZE

In view of the lack of Spanish studies that analyse the economic impact of Idiopathic Pulmonary Fibrosis (IPF) according to deterioration in the predicted forced vital capacity (FVC), and as this is a prospective observational study, it was decided to observe all the patients with IPF that meet the inclusion/exclusion criteria during the inclusion period. Based on the investigation into the viability of recruitment, we expect to include approximately 200 patients.

The primary objective of the study is to compare the economic impact according to FVC levels. This would mean opting for a balanced sample size for the three comparison groups. However, knowing the approximate patient prevalence according to predicted FVC (5-11% predicted FVC <50%, 51-73% predicted FVC 50-80%, and 22-38% predicted FVC >80%) (*8*), and the sponsor's internal data, we have estimated to find:

- 10-22 patients with predicted FVC <50%.
- 102-143 patients with predicted FVC 50-80%.
- 43-76 patients with predicted FVC >80%.

Depending on the final distribution obtained in terms of number of patients for each comparison group and given the exploratory nature of this study, it is expected that comparisons between some groups will have a descriptive approach, although the expected comparison analyses will be carried out as stated in this protocol (explorative statistical model if sample size allows). Although the expected number of patients with predicted FVC <50% is small, it should at least provide first insights into the costs within this patient subgroup.

In view of the lack of previous data on the cost of the disease according to the study's primary endpoint in Spain, this will be the first Spanish cost comparison study according to predicted FVC.

9.6 DATA MANAGEMENT

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The electronic Case Report Forms (eCRFs) will include programmable edits to obtain immediate feedback if data are missing (also negative answers, unknown), out of range, illogical or potentially erroneous. These rules may encompass simple checks such as range validation or presence/absence of data. Concurrent manual data review may be performed based on parameters dictated by the DMP. Ad hoc queries to the sites may be generated and followed up for resolution. A source data quality audit may be initiated to ensure that the data in the database is accurate.

The database will be housed in a physically and logically secure computer system maintained in accordance with a written security policy. The system will meet the standards of the

International Committee on Harmonization guideline E6R1 regarding electronic study data handling. Patient confidentiality will be strictly maintained.

9.7 DATA ANALYSIS

A statistical analysis plan will be drawn up specifying all the analyses to be performed. However, a summary of the anticipated statistical analysis is provided below.

A descriptive analysis will be performed of all the variables recorded for the study population. For the continuous variables, we will calculate the mean, the standard deviation, the 95% confidence interval (CI) of the mean, the median, max. and min. and the interquartile range (IQR). Categorical variables will be presented as absolute and relative frequencies (percentages) and 95% CIs.

For all exploratory statistical tests, a significance level alpha of 0.05 will be assumed. The data analysis will be performed by using the SAS statistical package, version 9.4 or later.

Missing values will not be imputed in the main analysis. However, if considering only observed values for an analysis is felt to bias the results. post-hoc sensitivity analyses including imputation techniques might be applied.
For each questionnaire, its indications will be followed (for example, calculating the score considering the number of available items or missing all data).

9.7.1 Main analysis

a) To compare the economic impact of Idiopathic Pulmonary Fibrosis (IPF) according to predicted FVC% (FVC<50%, FVC 50-80%, FVC>80%), in adult patients through the estimation of annual direct and indirect costs associated with the disease.

Annual direct IPF-related costs (primary and secondary care visits, outpatient visits, emergency visits -primary care and hospital-, hospitalisations, ICU with and without intubation, outpatient tests and other examinations, pharmacological and non-pharmacological treatments, orthopedic material, use of transport, formal caregiver, formal social services, economic aid and structural adaptations) and indirect costs (days off work and informal caregiver) will be quantified for each patient over the follow-up period of 12 month.

The direct costs over the 12 month follow-up period will be quantified by multiplying the recorded natural units of use of resources by the unit costs obtained by consulting Spanish databases or similar studies. The opportunity cost method will be used to calculate informal care costs. The indirect costs will be estimated by applying salary costs based on the latest data published by the Spanish Instituto Nacional de Estadística (INE) (*6*) from the salary structure survey, adjusted to age.

In order to obtain the most recent unit costs, they will be consulted at the time of the analysis. All costs will be expressed in euros for the year 2018, updating as necessary the costs from previous periods according to the cumulative consumer price index (CPI) since the publication of the cost up to December 31, 2017.

For the primary objective of the study, the characteristics of the subpopulations defined by the categorisation of the deterioration in predicted FVC (FVC <50%, FVC 50-80%, FVC >80%) at the time of inclusion (T=0) will be described. The Chi-square test will be used for the comparisons of the qualitative (categorical) variables. For the comparisons of the quantitative (continuous) variables, analysis of variance (ANOVA) or Kruskal-Wallis tests will be performed. Results of all statistical tests must be interpreted purely exploratorily.

9.7.2 Further analysis

The following analyses will be performed according to secondary objectives.

a) To estimate the QoL of patients with IPF according to predicted FVC% through the SGRQ and EQ-5D-5L questionnaires and the Barthel index.

   For the SGRQ, the mean, the SD, the 95% CI of the mean, the median, max and min and the IQR will be calculated from the scores obtained on the three scales (symptoms, activity, impact) and from the total score in each subpopulation (FVC <50%, FVC 50-80%, FVC >80%).

   For the EQ-5D-5L questionnaire, as the data are not continuous but ordinal, the information will be presented in terms of absolute and relative frequencies for each subpopulation (FVC <50%, FVC 50-80%, FVC >80%) by levels in each dimension. The EQ-5D-3L comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems

   A missing response in either of the questionnaires will exclude the patient from the specific analyses.

b) To explore the determinants of costs and QoL in patients with IPF according to predicted FVC%

   If sample size allows, bivariate exploratory methods e.g. analysis of variance (ANOVA), Kruskal-Wallis test will also be applied to explore predictors of costs and quality of life for each study subpopulation (FVC <50%, FVC 50-80%, FVC >80%) such as sociodemographic and clinical variables collected.

   Taking into account that the expected final number of patients of the FVC <50% stratum could be small, with less of 20 patients, and the limitations that a multivariate analysis might have, an exploratory bivariate analysis could be performed with those variables considered as relevant.

   Some variables may be categorised to provide practical information in the clinical setting.

   If sample size allows, multivariate exploratory analyses (e.g. generalized linear models) will be applied which include costs and quality of life as dependent variables, and the explanatory variables will be discussed based on previous bivariate analyses and clinical

relevance. Sample size and constraints imposed by the analysis models may prevent to include all variables of interest in this setting.

c) To characterize acute IPF exacerbations (frequency and cost) according to FVC% predicted level
The total number of acute IPF-related exacerbations as well as the use of resources and costs associated with the events during one year according to the predicted FVC at the time of inclusion (FVC <50%, FVC 50-80%, FVC >80%) will be described.

For the quantitative (continuous) variables, we will calculate the mean, the SD, the 95% CI of the mean, the median and the IQR. Qualitative (categorical) variables will be presented as absolute and relative frequencies (percentages).

d) To describe the cost and QoL variation associated with the lung capacity deterioration (change among the FVC % predicted level along 12 month)

Descriptive analyses will be carried out of direct and indirect costs and patient quality of life according to the change in FVC (<-10%, from -10% to -5%, and >-5%) between T0 and T12.

For the quantitative (continuous) variables, we will calculate the mean, the 95% CI, the median and the IQR. Qualitative (categorical) variables will be presented as absolute and relative frequencies (percentages).

When sample size is minimum, subgroup analyses will be explored for the following subgroup variables (or others, if deemed appropriate, defined in the SEAP):
- % FVC predicted in T0 (FVC >80%, FVC 50-80% and FVC <80%)
- antifibrotic treatment vs non antifibrotic treatment
- one acute IPF exacerbation vs. more than one acute IPF exacerbation during study period.

e) To assess the QoL of the caregiver through the Zarit Burden Interview questionnaire.
Caregiver quality of life will be explored using the Zarit questionnaire. Caregiver quality of life will be assessed at visits T0, T6 and T12.

We will report the responses to the 22 items that make up the instrument, as well as the total score for the questionnaire. The distribution of caregiver burden will be described according to the following categories (17):

little or no burden	→	Zarit score ≤21
Mild to moderate burden	→	Zarit score >21 and ≤40
Moderate to severe burden	→	Zarit score >40 and ≤60
Severe burden	→	Zarit score ≥61

9.8 QUALITY CONTROL

To improve and secure data quality, automatic data checks upon data entry will be done within the eCRF. In the eCRF, plausible ranges of values for numeric data entries as well as logical data entries and listings will be provided for each entry field. Based on this, checks on completeness and plausibility will be performed upon data entry in the eCRF.

Validity of data entry thus is ensured by integrated validation checks performed by the system, indicating missing or implausible entries to the document list or investigator. All corrections will be visible from the systems audit trail.

No regular source data verification is planned in this study. However, in case of decreasing compliance (i.e. of missing data, data discrepancies, protocol violations, etc.) a for-cause audit or risk-based monitoring visit will be performed.

Telephone Monitoring is planned in this study. A Monitoring Plan will be created to describe the telephone monitoring procedures.

9.9 LIMITATIONS OF THE RESEARCH METHODS

The intention of this NIS is to collect data about direct and indirect costs related to IPF in a real world setting. A NIS is the most suitable instrument for obtaining information about the use of resources everyday clinical practice and thus for investigating prospectively questions in everyday clinical practice.

Consecutive enrolment will be employed to minimize selection bias. The entry criteria are non-restrictive which will permit the enrolment of a broad patient population. Selection bias may also occur due to loss to follow-up.

There are several different types of bias that could influence the data collection and analysis, such as selection, information, and channelling bias. Selection bias could occur at the site level and the patient level. To minimize the site level selection bias, the goal is to have participating sites that have access to patients from all the stratums (FVC<50%, FVC 50-80%, FVC>80%). To minimize selection bias at the patient level, consecutive enrolment is performed. Information bias will be minimized by the use of standard eCRF, questionnaire and physicians' training on the study protocol.

An additional limitation is related with the setting selected of the study, that could lead to a under estimation of the healthcare resources consumed as Primary Care resource use or resource related with visits to another hospital or specialist will not be collected. Comorbidities that could impact resource utilization may not be fully captured, and may vary by subgroup
Other limitation is related to the sample size in some subgroups, this factor may limit some testing. And also, even though include 25 Spanish hospitals, study sites may not be fully representative of the Spanish IPF population.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

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.

9.10.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via remote data capture. Data will be captured via a web-based Electronic Data Capturing system. The site staff will enter and edit the data via a secure network, with secure access features (username, password and secure identification – an electronic password system). A complete electronic audit trail will be maintained. Patients must not be identified on the eCRF by name. Appropriately coded identification (i.e. Patient numbers) must be used. All patient/caregiver questionnaires will be paper-based and will be left at the site upon completion by the patient.

9.10.2.1 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.

The following source documents are expected in this study:

To be completed by the physician:
- Patient demographics and medical data

To be completed by the patient along the study:
- Patient diary

To be completed by the patient at visit T0, T6 and T12:
- SGRQ
- EQ-5D-5L

To be completed by the caregiver at visit T0, T6 and T12:
- Zarit Burden Interview

9.10.2.2 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 9.10.2.1.

9.10.3 Completion of study

The EC/competent authority in each participating EU member state needs to be notified about the end of the study (last patient / patient out, unless specified differently in Section 9.2) or early termination 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 Harmonised 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 the patient´s physician

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.

Insurance Cover: as non-interventional study and according the local regulations the insurance policy is not applicable.

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.

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 GEP and GPPand 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.

Prior to patient's caregiver participation in the study, written informed consent must be obtained from them according to GEP and GPPand 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 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 and patient's caregiver (if applicable) 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 and patient's caregiver (if applicable) must be informed that his / her medical records may be examined by authorised 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.

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, i.e. the competent authority (CA).

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 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)
The term Adverse Event of Special Interest (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.

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 and non-drug related nature. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI 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:
- all adverse drug reaction (ADRs) (serious and non-serious),
- all AEs with fatal outcome

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

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria in the (e)CRF.

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into 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
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:

Type of Report	Timeline
All **serious ADRs** associated with a BI drug taken for the disease in scope of the study	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to a BI drug taken for the disease in scope of the study	immediately within 24 hours
All **non-serious ADRs** associated with a BI drug taken for the disease in scope of the study	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.

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 taken for the disease in scope of the study other than the 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

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.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

The stand-alone documents for this non-interventional study are:
- Patient Informed Consent Form
- Patient's Caregiver Informed Consent Form
- Statistical Analysis Plan (SAP)
- Data Management Plan (DMP)
- Monitoring Plan (MP)
- Serious Adverse Event Report in Non-Interventional Studies (NIS (S)AE Form)
- Pregnancy Monitoring Form
- Publication Plan

All of the above documents will be archived in the Trial Master File in its original master version.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. ADDITIONAL INFORMATION

1. ***Patient diary***
2. ***SGRQ questionnaire***
3. ***EQ-5D-5L questionnaire***
4. ***Zarit Burden Interview questionnaire***
5. ***Barthel questionnaire***

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