Non-interventional Study Protocol

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Brief lay title	NI PASS of Nintedanib in IPF in Argentina
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Medicinal product:	Nintedanib (OFEV®)
Product reference:	Approved in Argentina by ANMAT Disposition 8067/16
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Marketing authorisation holder(s):	Boehringer Ingelheim S.A. Juana Azurduy 1534 Ciudad de Buenos Aires ; Argentina
Joint PASS:	No
Research question and objectives:	Main research question is to study the safety and effectiveness of nintedanib in 2 selected referral centers in Argentina
Country(-ies) of study:	Argentina
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Marketing authorisation holder(s):	Boehringer Ingelheim S.A. Juana Azurduy 1534 Ciudad de Buenos Aires ; Argentina
In case of PASS, add: **MAH contact person:**	*In case of PASS, insert name of contact person for this PASS protocol submission (if this a joint PASS, only one person should be mentioned)*
In case of PASS, add: **<EU-QPPV:>**	*In case of PASS, insert name and contact details of the EU-QPPV or his/her delegate*
In case of PASS, add: **<Signature of EU-QPPV:>**	*In case of PASS, insert: <The signature of the EU-QPPV is provided electronically>*
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2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALAT	Latin American Thorax Association
ALT	Alanine aminotransferase
ANMAT	National Administration of Drugs Food and Medical Technology
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BID	Bis in die (twice daily)
CRF	Case Report Form
DLCO	Carbon monoxide Diffusion Capacity
EU	European Union
ERS	European Respiratory Society
FDA	Food and Drug Administration
FGFR	Fibroblast growth factor/receptor
FVC	Forced Vital Capacity
GGT	Gamma-glutamyltransferase
GPP	Good Pharmacoepidemiology Practice
HRCT	High resolution computerized tomography
IEC/ IRB	Independent Ethics Committee / Institutional Review Board
IPF	Idiopathic Pulmonary Fibrosis
JRS	Japanese Respiratory Society
LFT	Liver Function Test
MAH	Marketing Authorization Holder or Sponsor
NAC	N-acetyl cysteine
PDGFR	Platelet derived growth factor/receptor
PGR	Patients global rating scale
SAE	Serious Adverse Event
SGRQ	Saint Georges Respiratory Questionnaire
SOP	Standard Operating Procedure
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Event
TGFB	Transforming growth factor ß
ULN	Upper Limit of Normal
US	United States of America
VEGFR	Vascular endothelial growth factor/receptor

3. RESPONSIBLE PARTIES

MOH main responsible parties are listed in the initial protocol title page. Contact details and the list of all investigators will be kept in a stand-alone document listed in Annex 1 available upon request.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: OFEV®			
Name of active ingredient: Nintedanib			
Protocol date: 02Feb2017	**Study number:**	**Version/Revision:** Version 1.0	**Version/Revision date:**
Title of study:	Post Authorization Safety Study of Nintedanib in the Treatment of Patients with Idiopathic Pulmonary Fibrosis in Argentina. Version 1.0 dated 02Feb2017 Main Author: Laura Cornejo		
Rationale and background:	Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease characterized by fibrosis of the interstitium and progressive loss of lung function with shortened lifespan. A greater understanding of the pathogenesis of IPF and thoroughly designed clinical trials have changed the treatment landscape of IPF. Nintedanib, a potent inhibitor of tyrosine kinases has reduced the decline in forced vital capacity (FVC), which is consistent with a slowing of disease progression and has obtained marketing authorization approval in US, EU, Argentina and other countries. The product was registered in Argentina through the orphan drug disposition that requires a real world observational registry assessing the orphan drug safety and effectiveness.		
Research question and objectives:	The main objective of this study is to describe the safety and effectiveness of nintedanib in 2 selected referral centers in Argentina. The primary epidemiological objective for this study is to study the baseline characteristics of the population with IPF that initiate nintedanib in two centers in Argentina and the primary safety objective is to evaluate the safety of nintedanib through the incidence of all adverse events. Secondary objective is to study the effectiveness through the patient global rating (PGR) scale and the annual rate of decline in FVC.		

Study design:	Non interventional study based on newly collected data Patients newly initiating nintedanib will sign a consent form. Once the patient has signed the informed consent, the treating physician will complete a baseline case report form and follow the patients by the usual standards of care. Patients included in the registry are expected to be followed up to death, lung transplant, suspension of treatment, lost to follow up or ANMAT termination of the registry. Study duration is estimated to be from the initial approval of nintedanib and will continue up to 5 years.
Population:	The study population comprises all patients with idiopathic pulmonary fibrosis (IPF) newly initiatingtreatment with nintedanib, as per routine clinical practice.
Variables:	The Primary safety outcome is the incidence of all adverse events Secondary effectiveness objectives and variables are: Patient global rating (PGR) scale and annual rate of decline in FVC.
Data sources:	Patients' data will be collected from the medical records on paper CRFs at baseline and every 6 months.
Study size:	The sample of patients is based on all the consecutive patients that will receive nintedanib from the two selected referral sites.
Data analysis:	Only descriptive statistics will be used in the analysis of this study. All enrolled IPF patients who have at least single dose of studied medicinal product nintedanib described in the protocol will be the population for analysis of the primary safety objective. Effectiveness analyses will be performed in all patients that at least have one follow up contact. Analysis will be performed yearly at each mandatory interim report and at end of study.
Milestones:	Start of data collection is estimated to start at the end of 1stQ 2017 Reporting to Ministry of Health will be performed on a yearly basis since the local marketing authorization application of the drug and registry will be extended until ANMAT decides that it is no longer needed.

5. AMENDMENTS AND UPDATES

This study is mandated by the ministry of health division ANMAT in Argentina and based on an initial post authorization plan to monitor efficacy, effectiveness and safety of nintedanib that was an integral part of the marketing authorization application. Therefore any potential non administrative amendment will be based on amendments to such plan that will need to be submitted and approved by ANMAT. All potential amendments to the plan will be introduced as an amendment to the current protocol that will be prepared by the Marketing Authorization Holder/Sponsor.

So far no amendments have been made to the initial plan.

Number	**Date**	**Section of study protocol**	**Amendment or update**	**Reason**
NAP	NAP	NAP	NAP	NAP

6. MILESTONES

Study milestones are given in the following table and depend on ANMAT decision regarding the need for study continuity

Milestone	**Planned Date**
IRB/IEC approval	Not applicable
Start of data collection	Estimated Q1 2017
End of data collection	Estimated Q1 2022
Interim reports	Every 12 month Report (data cutoff 9 months and reporting 12 months after drug approval) First interim report is expected on June 2018.
Final report of study results:	3 months after end date

7. RATIONALE AND BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a chronic lung disease of unknown etiology characterized by fibrosis of the interstitium and characterized by worsening dyspnea, progressive loss of lung function with shortened lifespan and average life expectancy of 2-3 years[1].

Over the years, a number of pharmacologic strategies, without solid evidence demonstrating a beneficial impact on the disease course, have been used to treat IPF. The previously held theory that inflammation was the predominant underlying feature of IPF led to the use of corticosteroids and immunosuppressive therapy as usual care. However, a greater understanding of the pathogenesis of IPF and thoroughly designed clinical trials have changed the treatment landscape of IPF[2-3].

The pathogenesis of IPF is thought to involve activation of cell signaling pathways through pro-fibrotic growth factors, including platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF). Nintedanib (formerly known as BIBF1120) is a potent intracellular inhibitor of tyrosine kinases, which targets the Fibroblast Growth Factor Receptor 1 and 3 (FGFR - 1 / 3), the Platelet-Derived Growth Factor Receptor α and β (PDGFR α and ß), and the Vascular Endothelial Growth Factor Receptor 1, 2 and 3 (VEGFR 1-3)[4-5]. The preventive and therapeutic effects of nintedanib were clearly demonstrated in a mouse model of pulmonary fibrosis induced by BLM and silica.[4-6].

To evaluate the efficacy and safety of four different doses of nintedanib in patients with IPF, a randomized, double-blind, placebo-controlled, Phase II trial known as the TOMORROW trial was conducted[7]. This 12-month, phase 2 trial included a total of 432 patients with IPF who underwent randomization to receive one of four doses of nintedanib (50 mg once a day, 50 mg twice a day, 100 mg twice a day, or 150 mg twice a day) or placebo. The primary end point was the annual rate of decline in forced vital capacity (FVC). Secondary end points included acute exacerbations, quality of life (measured with the St. George's Respiratory Questionnaire [SGRQ]), and total lung capacity. . In the group receiving 150 mg of nintedanib twice a day, FVC declined by 0.06 liters per year, as compared with 0.19 liters per

year in the placebo group, a 68.4% reduction in the rate of loss with nintedanib (P = 0.01 with the hierarchical testing procedure). This dose also resulted in a lower incidence of acute exacerbations, as compared with placebo (2.4 vs. 15.7 per 100 patient-years, P = 0.02) and a small decrease in the SGRQ score (assessed on a scale of 0 to 100, with lower scores indicating better quality of life) as compared with an increase with placebo (-0.66 vs. 5.46, P = 0.007). Gastrointestinal symptoms (which led to more discontinuations in the group receiving 150 mg twice a day than in the placebo group) and increases in levels of liver aminotransferases were more frequent in the group receiving 150 mg of nintedanib twice daily than in the placebo group[7].

As a follow up in the development program two replicate 52-week, randomized, double-blind, phase 3 trials (INPULSIS-1 and INPULSIS-2) were performed to confirm the efficacy and safety of 150 mg of nintedanib twice daily as compared with placebo in patients with IPF[8-9]. The primary end point was the annual rate of decline in forced vital capacity (FVC) and key secondary end points were the time to the first acute exacerbation and the change from baseline in the total score on the St. George's Respiratory Questionnaire, both assessed over a 52-week period. A total of 1066 patients were randomly assigned in a 3:2 ratio to receive nintedanib or placebo. The adjusted annual rate of change in FVC was -114.7 ml with nintedanib versus -239.9 ml with placebo (difference, 125.3 ml; 95% confidence interval [CI], 77.7 to 172.8; P<0.001) in INPULSIS-1 and -113.6 ml with nintedanib versus -207.3 ml with placebo (difference, 93.7 ml; 95% CI, 44.8 to 142.7; P<0.001) in INPULSIS-2. In INPULSIS-1, there was no significant difference between the nintedanib and placebo groups in the time to the first acute exacerbation (hazard ratio with nintedanib, 1.15; 95% CI, 0.54 to 2.42; P=0.67); in INPULSIS-2, there was a significant benefit with nintedanib versus placebo (hazard ratio, 0.38; 95% CI, 0.19 to 0.77; P=0.005). The most frequent adverse event in the nintedanib groups was diarrhea, with rates of 61.5% and 18.6% in the nintedanib and placebo groups, respectively, in INPULSIS-1 and 63.2% and 18.3% in the two groups, respectively, in INPULSIS-2 [8-9].

To obtain an overall estimate of the treatment effect of nintedanib 150 mg twice daily (bid), pooled and meta-analyses of data from these three trials were conducted[10]. 1231 patients (nintedanib n = 723, placebo n = 508) were included in the pooled analysis. Adjusted annual rate of decline in FVC was -112.4 mL/year with nintedanib and -223.3 mL/year with placebo

(difference: 110.9 mL/year [95% CI: 78.5, 143.3]; p < 0.0001). The hazard ratio for time to first acute exacerbation was 0.53 (95% CI: 0.34, 0.83; p = 0.0047). Adjusted mean change from baseline in SGRQ score at week 52 was 2.92 with nintedanib and 4.97 with placebo (difference: -2.05 [95% CI: -3.59, -0.50]; p = 0.0095). Hazard ratios for time to all-cause and on-treatment mortality were 0.70 (95% CI: 0.46, 1.08; p = 0.0954) and 0.57 (95% CI: 0.34, 0.97; p = 0.0274), respectively, in favor of nintedanib. The meta-analysis was generally consistent with the pooled analysis. Diarrhea was the most frequent adverse event in the nintedanib group (61.5% of patients treated with nintedanib versus 17.9% of patients treated with placebo). Nintedanib has a beneficial effect on slowing disease progression in patients with IPF[10]. Data on efficacy and safety of nintedanib have been proved in real world experiences[11] and in the subset of patients with FVC ≤ 50% of predicted value[12].

These trials led to the US Food and Drug Administration (FDA) approval of Nintedanib in 2014 and by the European Commission (EC) in 2015 for this patient population and to the approval under orphan drug indication by the Health Authorities (ANMAT) of the ministry of health from Argentina in 2016. The orphan drug approval disposition 4622/12 of Argentina requires that the pharmaceutical company that has been granted the marketing application approval perform a monitoring plan to assess safety, and effectiveness of the newly approved drug in order to determine the adequate risk/benefit ratio in common clinical practice. This mandatory regulatory requirement motivates the design of the current observational intensive pharmacovigilance and effectiveness study of Nintedanib in patients with IPF in Argentina.

8. RESEARCH QUESTION AND OBJECTIVES

Main research objective is to study the safety and effectiveness of nintedanib in 2 selected referral centers in Argentina.

The first primary objective for this study is to describe the baseline characteristics of the population with IPF that newly initiate nintedanib in the context of common clinical practice.

The second primary objective for this study is to evaluate the safety of nintedanib in the context of common clinical practice on the basis of the following endpoint:

- Incidence of all adverse events

The secondary objective of this study is to evaluate the effectiveness of nintedanib in the context of common clinical practice in Argentina on the basis of the following endpoints:

- Subjective patient status assessment through the Patient Global Rating (PGR) scale.
- Annual rate of decline in forced vital capacity (FVC).

9. RESEARCH METHODS

9.1 STUDY DESIGN

Non-interventional study based on newly collected data (registry) The study population comprises all patients with idiopathic pulmonary fibrosis (IPF) that have received the indication for treatment with nintedanib, for the first time (new users) according to local laberlin the two selected referral centers in Argentina.

The Health Authority in Argentina (ANMAT) has granted nintedanib approval by the orphan drug disposition 4622/12 that requires the marketing authorization holder (sponsor) to perform a monitoring plan to assess safety and effectiveness of the newly approved drug in order to determine the adequate risk/benefit ratio in common clinical practice.

Treating physicians from the two selected referral sites, when deciding to prescribe nintedanib, should ask patients to sign a consent form that explains the expected risks and benefits of being treated with the drug. Once the patient has signed the informed consent, the treating physician will complete a baseline case report form and follow the patients by the usual standards of care, no scheduled patient visits will be required for the conduct of this study. However follow-up data will be gathered every 6 month period from the start of treatment in order to gather yearly vital status information and the nearest FVC.

Patients included in the registry are expected to be followed up to death, lung transplant, suspension of treatment, lost to follow-up or ANMAT termination of the registry. Study duration will extend from the initial approval of nintedanib by ANMAT, and will continue until ANMAT decides that this registry is no longer needed, or for a maximum of 5 years,at this time point, the present study will terminate, ongoing patients will be censored and no further data will be collected.

9.2 SETTING

Patients with idiopathic pulmonary fibrosis (IPF) that have received the indication for treatment with nintedanib, for the first time (new users) as per routine clinical practice in the two selected referral sites, are eligible for observation in this cohort registry type study if the following criteria are met:

9.2.1 Study sites

Two selected specialized referral sites will be used in this study.

9.2.2 Study population

Key inclusion and exclusion criteria for this study are:

Inclusion criteria:

- Signed informed consent form that has been submitted to ANMAT with the study plan
- Diagnosis of IPF based on the ATS/ERS/JRS/ALAT, 2011 guidelines[1]
- Patients who are newly initiators of treatment with nintedanib and have received at least one dose of nintedanib as per local label and clinical practice.

Exclusion criteria:

- Contraindication to receive nintedanib
- Patient is participating in a phase 2-3 clinical trial approved by ANMAT with an investigational product.

9.2.3 Study visits

Visits will happen as per clinical practice which will be approximately every 6 month from the start of treatment until the end of the study, treatment discontinuation,, lung transplantation or death. Data will be gathered from the medical records every 6 month period from the start of treatment until the end of study or treatment discontinuation.

9.2.4 Study discontinuation

Patients included in the registry are expected to be followed up to death, lung transplant, suspension of treatment, lost to follow up or ANMAT termination of the registry.

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

1. Emergence of any efficacy/safety information that could significantly affect continuation of the study, or any other administrative reasons, i.e. (ANMAT termination of the registry)
2. Violation of Good Pharmacoepidemiology Practice (GPP), Good Pharmacovigilance Practice Guidelines or current national regulations for the appropriate conduct of observational studies

9.3 VARIABLES

9.3.1 Exposures

Treatment recommendations for participating centers will be based on the approved label and are summarized below:

- The recommended dosage of nintedanib is 150 mg twice daily administered approximately 12 hours apart. Nintedanib capsules should be taken with food and swallowed whole with liquid. Nintedanib capsules should not be chewed or crushed because of a bitter taste. The effect of chewing or crushing of the capsule on the pharmacokinetics of nintedanib is not known. If a dose of Nintedanib is missed, the next dose should be taken at the next scheduled time. Patients should be advised not to make up for a missed dose. The maximum daily dosage of 300 mg should not be exceeded.
- In addition to symptomatic treatment, if applicable, the management of adverse reactions of Nintedanib may require dose reduction or temporary interruption until the specific adverse reaction resolves to levels that allow continuation of therapy. Nintedanib treatment may be resumed at the full dosage (150 mg twice daily), or at the reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage. If a patient does not tolerate 100 mg twice daily, discontinue treatment with Nintedanib.

- Dose interruption is necessary for aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation >3 times interrupt treatment. Once liver enzymes have returned to baseline values, treatment with Nintedanib may be reintroduced at a reduced dosage (100 mg twice daily), which subsequently may be increased to the full dosage (150 mg twice daily).
- Discontinue Nintedanib for AST or ALT elevations >5 times ULN or >3 times ULN with signs or symptoms of severe liver damage.

9.3.2 Outcomes

9.3.2.1 Primary outcomes

The primary epidemiological objective is to study the baseline characteristics of patients included in the registry. Demographic characteristics, co-morbidities and previous or concurrent treatment for IPF including but not limited to pirfenidone will be documented and described.

The primary safety objective is to collect all adverse events occurred in patients included in the registry.

9.3.2.2 Secondary outcomes

The secondary objective of this study is to evaluate the effectiveness of nintedanib on the basis of the following endpoints:

- Subjective patient status assessment through the Patient Global Rating (PGR) scale, which will be assessed in the date nearest to that of each year after start of treatment.

- Annual rate of decline in FVC, that will be assessed through the routine pulmonary function test performed in the date nearest to that of each year after start of treatment.

9.3.3 Covariates

The purpose of this study is mainly descriptive in nature as per a mandatory regulatory requirement. There are additional variables that will be captured during the study Baseline demographics; clinical comorbidities; Baseline FVC, DLCO and 6 minute walking test; previous treatment for IPF and concomitant treatment for IP. However, these variables are not planned to be considered as covariates in a strict sense since they will not be included in any analysis model related to endpoints of this study.

9.4 DATA SOURCES

Patients will be followed by the physician as per routine medical practice. There are no visits planned by protocol, nevertheless baseline and 6 month follow up data will be gathered from the medical records. When a primary or secondary endpoint is met the data will be extracted at the nearest routine 6 monthfollow up Patient data will be recorded from the medical records on paper CRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient medical records should be entered on the CRF as soon as they become available.

During treatment period, assessments will be routinely performed in accordance with current guidelines and local standard of care. When performed during the observational period, available results from the range of assessments described as end points in this registry will be documented on the CRF. Patients included in the registry are expected to be followed up to death, lung transplant, discontinuation of treatment, lost to follow up, ANMAT termination of the registry. For patients who complete the registry the study completion CRF should be completed. Clinical AEs, serious and non-serious, as well as safety data other than AEs as described in Section 8 will be recorded in the CRF during the total observation period.

9.5 STUDY SIZE

As this is a request by ANMAT the sample of patients is based on all the consecutive patients that will receive nintedanib. All patients that receive nintedanib from the two

selected referral sites are potential targets for inclusion. All patients will be followed up periodically according to local practice while they are on nintedanib therapy

9.6 DATA MANAGEMENT

The sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via paper CRFs. Physicians will be responsible for data entry into the CRFs. In the event of missing, discrepant or outlier data, sponsor will request data clarification from the physicians, which the physicians will resolve in the data clarification form.

Data will be periodically transferred in paper from the sponsor affiliate to the BI data management facility and sponsor standard procedures will be used to handle and process the transfer of these data.

Data base correction documentation will be maintained in the data base system audit trail. All data management will be performed according to sponsors standard systems and operating procedures (SOPs).

9.7 DATA ANALYSIS

All enrolled patients who have at least single dose of studied medicinal product nintedanib described in the protocol will be the population for analysis of the primary safety objective. All patients with at least one follow up contact will be the basis of the population for the secondary effectiveness analysis.

9.7.1 Main analysis

Descriptive statistics will be mainly used in the analysis. Categorical variables will be individually listed and summarized using counts and percentages of patients with 95% confidence interval calculation where appropriate. Continuous variables, will be presented using the number of patients (N), mean, standard deviation (SD), median, minimum (Min), maximum (Max), first and third quartiles, and number of observations, change and percentage change from baseline values (depending on the variables) with graphics and

statistical tables where appropriate. Kaplan Meir survival curves will be used where appropriate. No imputation is planned for missing data, besides usual survival handling (if appropriate) with censoring at the last observation time.

The primary epidemiological objective is to study the baseline characteristics of patients included in the registry. Demographic, disease related, co-morbidity and previous or concurrent treatment for IPF including but not limited to pirfenidone will be documented and described.

The primary safety objective will be to determine of all adverse events of nintedanib use. Also the causality, nature, frequency, severity, seriousness, outcome and timing of adverse events AEs will be summarized using the safety population and all the information related to the AEs (including system organ class and preferred term according to MedDRA) will be provided. Adverse events (AEs) will be graded according to the definitions outlined in section 8. All AEs will be displayed in summary tables, by system organ class and preferred term. The tables will present the number of patients for which the events occurred, and the rate of occurrence, expressed as a percentage of the number of patients in the safety population. Deaths, related serious AEs and those AEs leading to treatment discontinuation, will also be summarized using preferred term and system organ class. Analysis will be performed yearly at each mandatory report and at end of study. Statistical analysis and reporting of adverse events will concentrate on treatment emergent adverse events. Statistical analysis will be done in a descriptive mode. To this end, all adverse events that emerges during treatment having been absent pre-treatment, or worsens relative to the pre-treatment state with an onset up to a period of 28 days (inclusive) after the last dose of study medication will be considered ‘treatment emergent’ and will be assigned for evaluation.

Effectiveness analyses will be performed in all patients that at least have one follow up contact, and will be performed yearly at each mandatory report and at end of study, based on the following secondary objectives:

- Subjective patient status assessment through the Patient Global Rating (PGR) scale, which will be assessed at the nearest routine visit after every 6 month period from the start of treatment. PGR is a global rating of change scale where patients will subjectively rate their overall disease condition scored from -7 to +7. Mean and

median scores at each yearly visit will be tabulated together with their SD and first and third quartile.

- Annual rate of decline in FVC: will be assessed at the nearest routine visit after every 6 month period from the start of treatment in order to gather yearly vital status information and it will be calculated as: Follow up FVC – Baseline FVC, expressed in ml.

9.8 QUALITY CONTROL

Sponsor will be responsible for overall quality control of this observational registry. Sponsor will assign a study manager or equivalent to be in charge of the trial. To ensure good quality data investigators will receive prior training and material related to the study.
Physicians will be responsible for data entry into the CRFs. Data will be monitored through the data management facility and data clarifications forms sent to the investigators for resolution (see section 6.6). Applicable sponsor's SOP for post authorization safety studies will be followed. (001-MCS-90-140) Additional on-site monitoring may be performed if judged necessary by the sponsors study manager. Quality issues related to spirometry are discussed in next section 9.9.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This study is an observational post authorization safety registry that has therefore several limitations related to the type of study design with main focus in safety and secondarily in effectiveness in the context of common clinical practice (real world data). The main limitations are related to the following issues:

- Quality issues: The two selected sites will use different spirometers. In order to minimize potential errors in the FVC assessment the two selected sites will perform daily calibration of spirometers and appoint experienced staff for spirometry. Spirometry will be performed according to the criteria published by the American Thoracic Society and the European Respiratory Society[13]. The same table for normal predicted values will be used as described by the Working Party for Standardization of Lung Function Test of the European Respiratory Society [14]. Even

though two academic referral sites have been selected for this study, due to the potential variability in results, type of study design, small number of patients and progression of the disease no causality assessment can be made.

- Bias due to lack of control group: As there is no concurrent or historical control group in Argentina and taking into account that real world population receiving treatment may have different type of risk profile, data from this registry cannot be compared with other treatment data and only in with limitations to data from previous randomized controlled clinical trial.

- Disease misclassification: There is potential error in the diagnosis of IPF that needs to rule out fibrosis secondary to rheumatic disease, drugs, hypersensitivity pneumonitis, professional disease or other causes of pulmonary fibrosis. The two selected sites have experience in the assessment and diagnosis of this type of patient population, which will reduce this potential error.

- Missing data: Management of data from this study will contribute to reduce the amount of missing data. Also educational material will be distributed to patients and physicians in order to raise awareness related to adverse event reporting, drug discontinuation and management of dose changes

- Generalization of results: Only patients that have signed the informed consent will be included in the study. We expect that 95% of the patients in the two selected sites will accept to participate in the registry. This will reduce the probability of selection bias as all patients will be offered to participate in this mandatory registry. However the patients from these two academic centers may not be representative of all the patients with IPF in Argentina.

- Random error cannot be excluded

- Recall bias: As the visits are not programmed and follow up data accrual is scheduled every 6 months, there is potential for recall bias. Patients will be queried on their

experience in the last 6 months, so there is potential that data may not be recalled by the patient. However due to the characteristic of the disease we expect to gather the majority of clinically relevant data.

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), where applicable, 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, on paper .

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 reported on the CRFs 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 paper CRFs, the following data need to be derived from source documents:

- Patient identification (gender, date of birth)
- Patient participation in the study (substance, study number, patient number, date patient was informed)
- Dates of Patient's visits, including prescription of study medication
- Medical history (including study indication and concomitant diseases, if applicable)

- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (SAEs) (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results (in validated electronic format, if available)
- Conclusion of Patient's Participation in the study

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 9.10.2.19.10.2.1.

9.10.2.3 Storage of records

Storage of records need to comply with local requirements.

10. PROTECTION OF HUMAN SUBJECTS

This study is conducted under the orphan drug approval disposition 4622/12 of Argentina which requires that the pharmaceutical company that has been granted the marketing application approval perform a monitoring plan to assess safety and effectiveness of the newly approved drug in order to determine the adequate risk/benefit ratio in common clinical practice. This study will be conducted in alignment with the Guidelines for GPP published by the International Society of Pharmacoepidemiology and the laws and regulations of the country in Argentina.

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

Current study has been requested by the Health Authority in Argentina (ANMAT) who has approved the study plan and sample informed consent form that will be available to physicians who prescribe nintedanib in local language. As this study is part of a mandatory pharmacovigilance registry in Argentina, no additional independent ethics committee / institutional review board approval is needed by local regulations. The study regulatory authority is the Ministry of Health division of ANMAT in Argentina.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before he/she can start receiving nintedanib. By signing the form, the patient confirms that he/she has been informed about the expected benefits and risks of therapy with nintedanib, and that information regarding his/her treatment are requested by the Health Authorities, and agrees to anonymous data collection, and pooling of data with similar scientific data (if applicable).

It is the responsibility of the treating physician to obtain written informed consent from each patient receiving nintedanib. The patient or his/her legal representative will sign and date two copies of the consent form, one copy must be provided to the patient or the patient's legally authorized representative and another must remain in the treating physician´s archive.

10.2 STATEMENT OF CONFIDENTIALITY

The marketing authorization holder maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any marketing authorization holder location. Patient medical information obtained by this study is confidential. Data generated by this study will be provided to local health authorities as appropriate.

Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study. Reasons for discontinuation of treatment with the medicinal product or withdrawal from the study may include, but are not limited to, the following: Patient withdrawal of consent at any time; Patient is lost to follow-up; Administrative reasons. The decision for discontinuation from treatment lies with the treating physician in agreement with the patient's decision and is not regulated by this protocol.

The primary reason for early treatment discontinuation should be documented on the appropriate CRF page. Every effort should be made to obtain information on patients who discontinue treatment or withdraw from the study. Patients will not be followed for any reason after consent has been withdrawn.

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 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 authorisation or from occupational exposure. Conditions of use outside the marketing authorization include offlabel use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event is defined as any AE which

- results in death,

- is life-threatening,

- requires in-patient hospitalization, or

- prolongation of existing hospitalisation,

- results in persistent or significant disability or incapacity, or

- is a congenital anomaly/birth defect

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

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise 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 hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction

Adverse Event of Special Interest (AESI)

No AESIs have been defined for this study.

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11.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

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

Collection of AEs

The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorization. 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.

According to local regulation, all adverse events must be collected by the investigator in the CRF from signing the informed consent onwards until the end of the study:
This includes events also to be collected:

All AEs , 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.

Causal relationship will be judged to be as follows:

- Definite: There is temporal relationship between the investigational product administered and the AE, cannot be explained by other causes and has positive dechallenge and rechallenge.
- Probable: There is temporal relationship between the investigational product administered and the AE, unlikely to be explained by other causes and has positive dechallenge.
- Possible: There is temporal relationship between the investigational product administered and the AE, may be explained by other causes and dechallenge or rechallenge is unclear.
- All events that are definite, probable or possible will be considered related for reporting purposes.
- Not related: There is no temporal relationship between the investigational product administered and the AE and/or there are other causes that clearly explain the event.

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. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day) to Boehringer Ingelheim pharmacovigilance). 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 nintedanib	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to nintedanib	immediately within 24 hours
All **non-serious ADRs** associated with nintedanib	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 treating physician 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 physician should provide the information requested on the appropriate 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 other than nintedanib 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

As this study is performed due to regulatory requirements in Argentina, results of each interim analysis and final report need to be reported to ANMAT division of the Ministry of Health in Argentina. Even though this is not initially planned, the results of this study may be published or presented at scientific meetings based on sponsor's decision. The marketing authorization holder will comply with all requirements for publication of study results and authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the marketing authorization holder, except where agreed otherwise.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document Reference Number	Date	Title
1	TBD	DD Month YYYY	List of Sites and Investigators

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Post Authorization Safety Study of Nintedanib in the Treatment of Patients with Idiopathic Pulmonary Fibrosis in Argentina.

Study reference number: < Study number – TBD >

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☒	☐	9.3
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.2
	4.2.2 Age and sex?	☒	☐	☐	9.2
	4.2.3 Country of origin?	☒	☐	☐	9.2
	4.2.4 Disease/indication?	☒	☐	☐	9.2
	4.2.5 Duration of follow-up?	☒	☐	☐	9.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.3.3; 9.9
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:	☒	☐	☐	9.9
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9
7.3 Does the protocol address the validity of the study covariates?	☐	☐	☒	

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10.2

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7
10.2 Are descriptive analyses included?	☒	☐	☐	9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.5 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.6 Is sample size and/or statistical power estimated?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

No Additional annexes included.