Non-Interventional Study (NIS) Protocol

Document Number:	c34369089-02
BI Study Number:	1199-0449
BI Investigational Product(s):	Nintedanib (Ofev®)
Title:	Prospective observational investigation of possible correlations between change in FVC and change in cough or dyspnea scores using the living with pulmonary fibrosis questionnaire (L-PF) between baseline and after approximately 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype.
Brief lay title:	**INREAL** – N**in**tedanib for changes in dyspnea and cough in patients suffering from chronic fibrosing interstitial lung disease with a progressive phenotype in everyday clinical practice: a **real**-world evaluation
Protocol version identifier:	*2.0*
Date of last version of protocol:	*8 February 2021*
PASS:	No
EU PAS register number:	EUPAS38272
Active substance:	Nintedanib
Medicinal product:	Nintedanib
Product reference:	EMEA/H/C/003821
Procedure number:	n.a.
Marketing authorisation holder(s):	[redacted]
Joint PASS:	No
Research question and objectives:	**Primary objective:** The primary objective of this study is to investigate the correlation between changes from baseline at 52 weeks in FVC [% pred.] and changes from baseline at 52 weeks in dyspnea score [points] or cough score [points] as measured with the L-PF questionnaire over 52 weeks

	of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype (excluding IPF): – Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in dyspnea symptom score – Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in cough symptom score **Secondary objectives** – Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in dyspnea symptom score – Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in cough symptom score – Absolute change from baseline in L-PF cough symptom score at week 52 – Absolute change from baseline in L-PF dyspnea symptom score at week 52 Primary and secondary objectives will be analyzed for the treated set.
Country(-ies) of study:	Germany
Author:	[redacted]
Marketing authorisation holder(s):	[redacted]
Date:	*8 February 2021*

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2. LIST OF ABBREVIATIONS

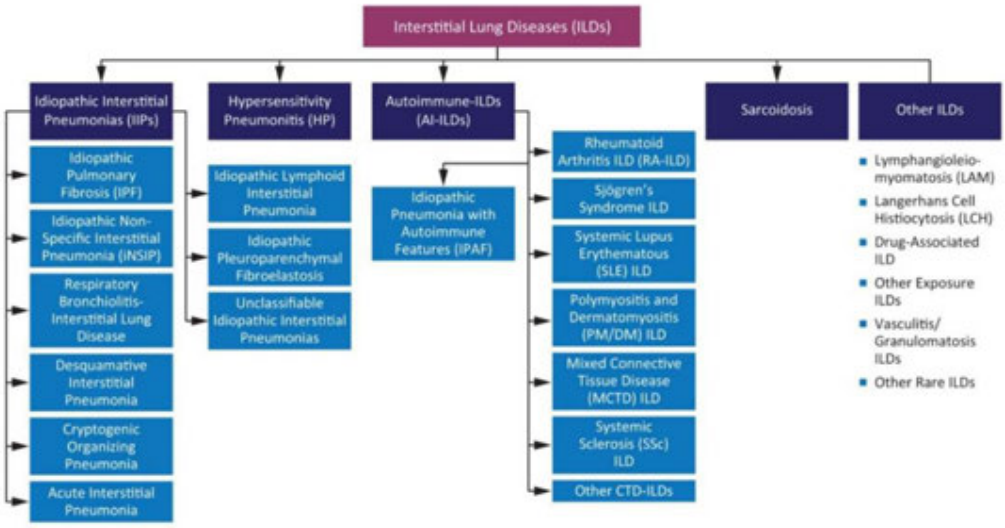
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event

3. RESPONSIBLE PARTIES

Function	Name	Contact details
NIS [redacted]	[redacted]	[redacted] phone: [redacted] [redacted]
Principle Investigator (Wissenschaftlicher Leiter)	[redacted]	[redacted]
CRO	[redacted]	[redacted]
Statisticians	[redacted] [redacted] (oversight)	[redacted] [redacted]

The study will be fully funded by Boehringer Ingelheim Pharma GmbH & Co. KG.

4. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Ofev®			
Name of active ingredient: L01XE31 Nintedanib			
Protocol date: 15-Dec-2020	**Study number:** 1199-0449	**Version/Revision:** 2.0	**Version/Revision date:** 8-Feb-2021
Title of study:	Prospective observational investigation of possible correlations between change in FVC and change in cough or dyspnea scores using the living with pulmonary fibrosis questionnaire (L-PF) between baseline and after approximately 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype. **INREAL** – N**in**tedanib for changes in dyspnea and cough in chronic PF-ILD patients in everyday clinical practice: a **real**-world evaluation		
Rationale and background:	The term interstitial lung disease (ILD) encompasses a large group of > 200 parenchymal pulmonary disorders, of which the majority are classified as rare. The most widely studied and most common ILD is Idiopathic Pulmonary Fibrosis (IPF). It is characterized by progressive fibrosis, lung scarring and a radiological pattern known as usual interstitial pneumonia (UIP). Several other ILDs (such as hypersensitivity pneumonitis (HP), rheumatoid arthritis-associated ILD (RA-ILD) and Systemic Sclerosis-ILD (SSc-ILD)) may present a progressive fibrosing phenotype as well. Given their overlapping clinical, radiological and pathological presentations, a terminology to describe these patients may be “chronic fibrosing ILD with a progressive phenotype”.  Figure 1 Classification of Interstitial Lung Disease (from [1]).		

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Progressive fibrosis of the lung parenchyma is self-sustaining and causes progressive deterioration in lung function, respiratory symptoms such as dyspnea. It therefore increases the risk of early death[2]. Cough and quality of life are also part of the progressive deterioration.

Scientific evidence shows from both the TOMORROW and the INPULSIS-1 and -2 trials that nintedanib is effective and its' side effects are manageable for the treatment of IPF in patients with different degrees of lung function impairment[3,4,5]. The available real-world data confirmed the safety and efficacy profiles of nintedanib in IPF that were established in clinical trials[6].

Furthermore, nintedanib was shown to significantly slow the annual rate of decline in the forced vital capacity (FVC) in patients with progressive fibrosing ILD[7]. In the INBUILD trial, which included ILD patients with a variety of underlying interstitial lung diseases, the magnitude of this benefit was similar to that previously described in the IPF population[5]. The treatment effect was consistent for patients with a UIP-like pattern as well as other patterns on HRCT, and also consistent across pre-defined subgroups of ILD diagnoses.

Insights from INBUILD further support the initial hypothesis that common traits in fibrotic mechanisms explain the clinical similarity of IPF and other fibrosing ILDs. In SENSCIS, patients suffering from SSc-ILD and treated with nintedanib were shown to have a reduced annual rate of decline in FVC vs patients in the placebo arm; though no clinical benefit of nintedanib was observed for other manifestations of systemic sclerosis[8].

To our knowledge, the effects of an antifibrotic therapy with nintedanib on the patient-reported outcomes (PRO) dyspnea or cough has only been investigated scarcely, especially in a real-world cohort.

This may partly be due to a lack of well-established, simple to use patient questionnaire that focuses on such symptoms. The living with pulmonary fibrosis questionnaire (L-PF) was used in the INBUILD trial. The complete L-PF questionnaire is a 44 item questionnaire with two modules: 1) symptoms (23 items) and 2) impacts (21 items). In this NIS, we will use the whole questionnaire. Its symptom part consists of three subdomains a) dyspnea b) cough c) fatigue (together 23 items). Each question is answered by the patient indicating one tick-box answer per question. Only one statement can be chosen. L-PF symptoms domain scores range from 0 to 100; the higher the score, the greater the impairment. An improved understanding of the patients' situation will benefit from further investigation of this instrument generated in a real-world setting.

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Results from INBUILD show that differences in the change of the score for cough and dyspnea from baseline to 52 weeks were statistically significant in favor of nintedanib, comparing treatment arm with placebo[1].. Those differences were small. A meaningful threshold ("MCID") has not been established for the L-PF questionnaire so far.

By applying the L-PF questionnaire and capturing the FVC, we want to further investigate whether there are correlations between change of FVC (ΔFVC: 52 weeks vs baseline) and change in cough or dyspnea score (Δcough, Δdyspnea: 52 weeks vs baseline) respectively, in this real-world patient population as well. Data from a real-world patient population may strengthen the data basis on this issue.

We are planning to include patients with chronic fibrosing ILD with a progressive phenotype excluding IPF patients. Regarding their specific form of chronic fibrosing ILD with a progressive phenotype, patients will be enrolled based on their phenotype and not on predetermined ILDs. – The study will include a pre-specified analysis of outcomes according to specific diagnoses, as the L-PF questionnaire was specifically developed for and validated in patients with chronic fibrosing ILD with a progressive phenotype, except IPF[1]. Furthermore, we plan to investigate a possible change in dyspnea and cough scores under nintedanib treatment, to answer the question whether nintedanib has a direct effect on PROs in a real-world patient population.

All patients will receive nintedanib according to standard of care, i. e. there will be no untreated comparison group in this study. Given the natural course of the disease, this poses a limitation in that results from the treated group will be difficult to interpret meaningfully in the absence of a reference group to demonstrate how the study outcomes appear in the absence of treatment in the real world setting.

In conclusion, this prospective, non-interventional study (NIS) aims to assess a possible correlation between the reduction of FVC decline and symptomatic burden under nintedanib treatment for 52 weeks in 100 patients with chronic fibrosing ILD with a progressive phenotype, measured as a possible change in dyspnea and cough scores from baseline using the L-PF questionnaire in a real-world patient population.

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Research question and objectives:	The primary objective of this observational study is to investigate changes in dyspnea or cough as measured with the L-PF questionnaire over 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype (excluding IPF), including a snapshot-analysis before last patient in, to evaluate a possible correlation between changes in FVC and L-PF (dyspnea and cough). This is the first RWE study in patients suffering from chronic fibrosing ILD with a progressive phenotype in Germany being treated with nintedanib. In addition, the German healthcare system is currently strongly supporting all necessary activities to fight the global Covid-19 pandemic with possible effects on the conduct of this study. In order to be able to identify and counteract possible restrictions due to these circumstances, a descriptive snapshot analysis is planned at the time of Last Patient In (LPI) in this study. With regard to the current COVID-19 pandemic, it was considered that all patients to be included into this NIS suffer from a severe medical condition and are in need of treatment according to their treating physician's assessment. The patients will be treated in usual care, no additional visits or examinations are demanded or required other than in clinical routine. So there is no additional risk for the patients in the COVID-19 pandemic caused by the study apart from their inherent risk as patients with a serious systemic disease affecting the lung. The study hypothesis is that in a one year observational study a correlation can be found between changes in lung function measured by FVC and the changes in the scores for dyspnea and cough of the L-PF questionnaire in ILD patients.		
Study design:	Observational study according to §4, section 23 and §67, section 6 German Medicines Act (NIS) based on newly collected data.		

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Population:	Patients to be recruited within this study have to have a physician diagnosed chronic fibrosing ILD with a progressive phenotype (except IPF), for which nintedanib is an indicated treatment. Before visit 1, patients must not have been treated with either nintedanib or pirfenidone, i. e., all patients are considered treatment naïve with regard to these antifibrotic treatments. • Only patients, for whom their treating physician has made the clinical decision to start nintedanib treatment (but not actually started treatment) independently of this study, are eligible to enter the study. • During the study, all patients are treated with nintedanib. For each individual patient, a treatment observation period of 52 weeks is aimed for. Handling of patient data with shorter observation period is going to be described in the SAP. <u>Inclusion criteria</u> • Adults ≥ 18 years at Visit 1 • Subjects must be contractually capable and mentally able to understand and follow the instructions of the study personnel • Physician's diagnosis of chronic fibrosing ILD with a progressive phenotype, except IPF • Treatment with nintedanib in INREAL will be the first and only prescription of any antifibrotic treatment for each individual patient within this observational study after a physician's decision being made for this treatment option earlier • Outpatients not currently hospitalized with a life expectancy > 12 months per investigator's assessment • Written informed consent prior to study participation • Current FVC measurement (taken within the last 3 months) available in the patient file • Women of childbearing potential must take appropriate precautions against getting pregnant during the intake of nintedanib.		

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	Exclusion criteria • Patients with contraindications according to SmPC • Prior use of antifibrotic treatment • Pregnant or lactating females • Lack of informed consent • Any physician diagnosed exacerbation of ILD in the patient's history, irrespective of time since event • Current diagnosis of lung cancer • Respiratory failure (pH < 7,35 and/or respiratory rate > 30/min) in the patient's history • Participation in a parallel interventional clinical trial Patients being spouse or lateral relatives to the second degree or economically dependent from the investigator		

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Variables:

Parameter	**Visit 1; baseline visit**	**Visit 2; (optional) ca. week 13**	**Visit 3; mid of observa-tion; ca. week 26***	**Visit 4; (optional) ca. week 39**	**Visit 5; end of observa-tion; ca. week 52**	**Visit 6 FU ca. week 52****
Informed Consent	X					
Inclusion / Exclusion Criteria	X					
Patient demographics (age, gender, height, and weight)	X					
Smoking history	X					
History of ILD, including ILD entity and HRCT pattern (where available in patient documentation)	X					
current DLCO measures (where available in patient documentation)	X	X	X	X	X	
Concomitant diseases / Comorbidities	X	X	X	X	X	
Past ILD therapies (6 weeks before visit 1)	X					
Current ILD related or other relevant concomitant medication	X	X	X	X	X	
FVC (mL and % pred.; if available in patient data)	X	X	X	X	X	X
Severity of disease as per the treating physician's estimation (if available in patient data)	X	X	X	X	X	X
L-PF questionnaire, completed by patient	X	X	X	X	X	X
Safety: Adverse Drug Reactions (serious and non-serious), fatal AEs, pregnancy	X	X	X	X	X	X

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Parameter	**Visit 1; baseline visit**	**Visit 2; (optional) ca. week 13**	**Visit 3; mid of observation; ca. week 26***	**Visit 4; (optional) ca. week 39**	**Visit 5; end of observation; ca. week 52**	**Visit 6 FU ca. week 52****
Rationale for treatment discontinuation (if applicable)		X	X	X	X	
Further treatment options yes/no (as applicable		X	X	X	X	X
Intention to continue or discontinue treatment with nintedanib after the study (yes/no)		X	X	X	X	
Survival data						X

* after 26 weeks of observation for each individual patient

** if available and/or patients is willing to perform, phone contact acceptable

In addition to the mandatory visits, i.e. Visit 1 (baseline), Visit 3 (mid of observation; 26 weeks after baseline) and Visit 5 (end of observation) and Visit 6 (Follow-up 52 weeks after baseline), optional study visits will be enabled between V1 and V3 (V2) as well as between V3 and V5 (V4), each occurring about midway between V1 and V3 or V3 and V5, respectively. Therefore, patients will be seen by their study investigator at least every 6 months and up to every quarter of the observational period.

When optional visits are conducted, then the same parameters as in Visit 3 should be documented.

Each visit should take place not earlier than six weeks before and no later than six weeks after the planned visit date and thus reflect patients' and physicians' real-world experience.

Survival data are to be collected 52 weeks after inclusion for all patients - including those patients who drop out. Patients who discontinue the study before week 52 for any reason should be contacted for survival status and follow-up data at week 52 (visit 6). For all other patients, visit 5 and visit 6 are completed in the same visit.

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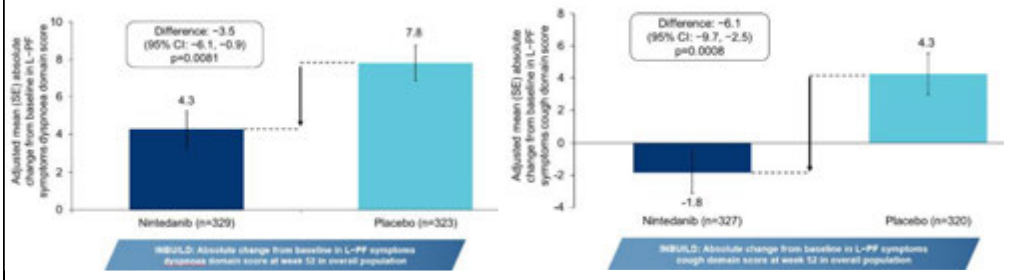
Data sources:	In this NIS, information about the effect of a treatment with nintedanib on differences in cough and dyspnea scores, measured via the L-PF questionnaire, will be collected and this information will be assessed in relation to FVC from these patients' medical files in patients with chronic fibrosing ILD with a progressive phenotype from 100 patients in about 20 study centers throughout Germany by specialized physicians (pulmonologists, rheumatologists) experienced in the treatment of ILD patients.		
Study size:	In the INBUILD trial, patient groups on placebo vs nintedanib therapy differed in both their loss of FVC and dyspnea and cough symptom scores in the L-PF questionnaire (Fig. 2; see below).  Fig. 2 Changes in dyspnea (left) and cough (right), respectively, seen in INBUILD ΔFVC, Δdyspnea and Δcough symptom scores from INBUILD (see Tab. 1 below) were applied to estimate sample sizes. Correlation between change from baseline FVC (both FVC in mL and FVC as % predicted) and change from both L-PF dyspnea symptom score and cough symptom score for the treated set at 52 weeks of treatment were ρ ≈ -0.3 for the Pearson correlation coefficient in the nintedanib arm (see Tab. 2 below)[11].		

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Data analysis:

Pearson correlation (change from baseline at week 52) between FVC and L-PF symptoms	Coefficient	95% Confidence interval Lower	Upper
L-PF symptoms dyspnoe score and …			
FVC in ml	-0.35	-0.45	-0.23
FVC (% predicted)	-0.37	-0.47	-0.26
L-PF symptoms cough score and …			
FVC in ml	-0.26	-0.37	-0.14
FVC (% predicted)	-0.26	-0.37	-0.14

Tab. 2 Pearson correlation for change from baseline to week 52 between FVC and L-PF symptoms scores in the nintedanib arm (Values were similar for the total population.)

Currently, a meaningful threshold ("MCID") for neither the cough nor the dyspnea domain of the L-PF has been published. However, should that information become available during the study, study results will be discussed in relation to the meaningful threshold ("MCID") values.

Given a correlation ρ between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in dyspnea symptom score as well between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in cough symptom score of approximately -0.3, then 84 patient data sets would be required for evaluation. Assuming an estimated drop-out rate of approx. 15 % 100 patients will have to be recruited for this study. With this patient number (N = 84) and the assumption of a Pearson correlation of -0.3, the overall type I error is protected at the two-sided 0.05 level with a power of 80 %.

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	Therefore 100 patients are planned to be recruited for this NIS by about 20 specialists, experienced in treating ILD patients, (e. g., pulmonologists and rheumatologists) throughout Germany. Each investigator will include ca. 5 consecutive patients for whom he/she had decided for a treatment with nintedanib before actual recruitment of the patient. The treatment decision will have to have taken place before actual recruitment of the patient. Due to the observational nature of the study, all analyses are exploratory. No weighting will be applied to either of the co-primary endpoints.		

5. AMENDMENTS AND UPDATES

V 1.0 dated 11 December 2020

V 2.0 dated 8 February 2021

- Changes as recommended by the ethics committee Medizinische Fakultät Heidelberg in chapter 9.2.3 Study visits
- Changes as recommended by the ethics committee Medizinische Fakultät Heidelberg in chapter 10 Protection of human subjects
- Two additional further outcomes added in chapter 9.3.2.3 Further Outcomes as recommended by TSTAT.

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	*Feb 2021*
Start of data collection	*Feb 2021*
End of data collection	*Feb 2023*
Final report of study results:	*Oct 2023*

7. RATIONALE AND BACKGROUND

The term interstitial lung disease (ILD) encompasses a large group of > 200 parenchymal pulmonary disorders, of which the majority are classified as rare. The most widely studied and most common ILD is Idiopathic Pulmonary Fibrosis (IPF). It is characterized by progressive fibrosis, lung scarring and a radiological pattern known as usual interstitial pneumonia (UIP). Several other ILDs (such as hypersensitivity pneumonitis (HP), rheumatoid arthritis-associated ILD (RA-ILD) and Systemic Sclerosis-ILD (SSc-ILD)) may present a progressive fibrosing phenotype as well.

Given their overlapping clinical, radiological and pathological presentations, a terminology to describe these patients may be “chronic fibrosing ILD with a progressive phenotype”.

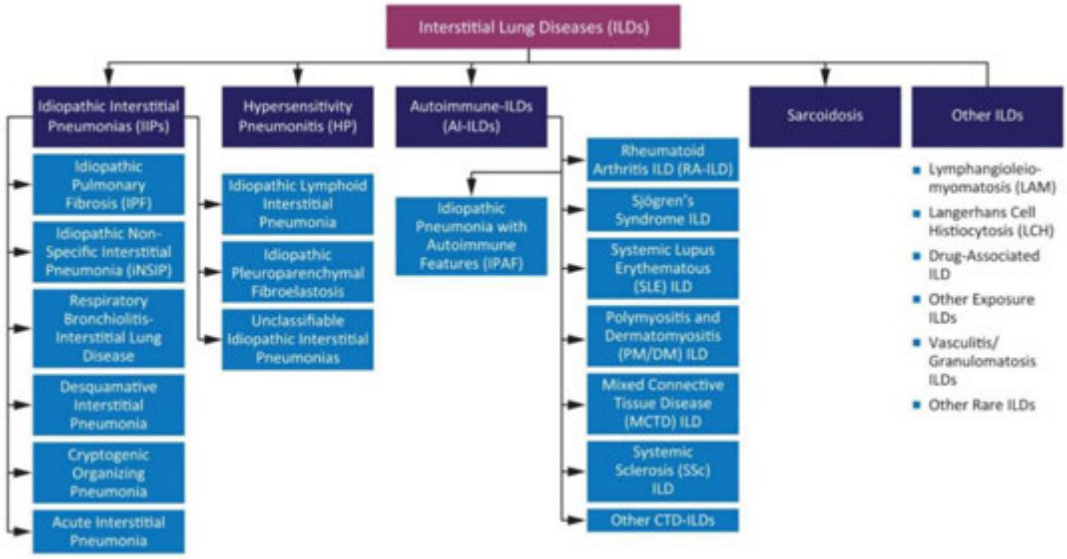

Figure 7:1 Classification of Interstitial Lung Disease (from [1]).

Progressive fibrosis of the lung parenchyma is self-sustaining and causes progressive deterioration in lung function, respiratory symptoms such as dyspnea. It therefore increases the risk of early death[2]. Cough and quality of life are also part of the progressive deterioration.

Scientific evidence shows from both the TOMORROW and the INPULSIS-1 and -2 trials that nintedanib is effective and it's side effects are manageable for the treatment of IPF in patients with different degrees of lung function impairment[3][4][5]. The available real-world data confirmed the safety and efficacy profiles of nintedanib in IPF that were established in clinical trials[6].
Furthermore, nintedanib was shown to significantly slow the annual rate of decline in the forced vital capacity (FVC) in patients with progressive fibrosing ILD[7]. In the INBUILD trial, which included ILD patients with a variety of underlying interstitial lung diseases, the magnitude of this benefit was similar to that previously described in the IPF population[5]. The treatment effect was consistent for patients with a UIP-like pattern as well as other patterns on HRCT, and also consistent across pre-defined subgroups of ILD diagnoses.

Insights from INBUILD further support the initial hypothesis that common traits in fibrotic mechanisms explain the clinical similarity of IPF and other fibrosing ILDs. In SENSCIS, patients suffering from SSc-ILD and treated with nintedanib were shown to have a reduced annual rate of decline in FVC vs patients in the placebo arm; though no clinical benefit of nintedanib was observed for other manifestations of systemic sclerosis[9].

To our knowledge, the effects of an antifibrotic therapy with nintedanib on the patient-reported outcomes (PRO) dyspnea or cough has only been investigated scarcely, especially in a real-world cohort.

This may partly be due to a lack of well-established, patient questionnaire that focuses on such symptoms. The living with pulmonary fibrosis questionnaire (L-PF) was used in the INBUILD trial. The complete L-PF questionnaire is a 44 item questionnaire with two modules: 1) symptoms (23 items) and 2) impacts (21 items). In this NIS, we will use the whole L-PF questionnaire. Its symptom part consists of three subdomains a) dyspnea b) cough c) fatigue (together 23 items). Each question is answered by the patient indicating one tick-box answer per question. Only one statement can be chosen. L-PF symptoms domain scores range from 0 to 100; the higher the score, the greater the impairment. An improved understanding of the patients' situation will benefit from further investigation of this instrument in a real-world setting.

Results from INBUILD show that differences in the change of the score for cough and dyspnea from baseline to 52 weeks were statistically significant in favor of nintedanib, comparing treatment arm with placebo[12]. Those differences were small. The meaningful threshold ("MCID") has not been established for the L-PF questionnaire so far.

By applying the L-PF questionnaire and capturing the FVC, we want to further investigate whether there are correlations between change of FVC (ΔFVC: 52 weeks vs baseline) and change in cough or dyspnea score (Δcough, Δdyspnea: 52 weeks vs baseline) respectively, in this real-world patient population as well. Data from a real-world patient population may strengthen the data basis on this issue.

We are planning to include patients with chronic fibrosing ILD with a progressive phenotype excluding IPF patients. Regarding their specific form of chronic fibrosing ILD with a progressive phenotype, patients will be enrolled based on their phenotype and not on predetermined ILDs. – The study will include a pre-specified analysis of outcomes according to specific diagnoses, as the L-PF questionnaire was specifically developed for and validated in patients with chronic fibrosing ILD with a progressive phenotype, except IPF[1]. Furthermore, we plan to investigate a possible change in dyspnea and cough scores under nintedanib treatment, to answer the question whether nintedanib has a direct effect on PROs in a real-world patient population.

All patients will receive nintedanib according to standard of care; i. e. there will be no untreated comparison group in this study. Given the natural course of the disease, this poses a limitation in that results from the treated group will be difficult to interpret meaningfully in the absence of a reference group to demonstrate how the study outcomes appear in the absence of treatment in the real world setting. However, data from this study will complement the data from INBUILD and INBUILD-ON, which can in turn provide context to this study.

In conclusion, this prospective, non-interventional study (NIS) aims to assess a possible correlation between the reduction of FVC decline and symptomatic burden under nintedanib treatment for 52 weeks in 100 patients with chronic fibrosing ILD with a progressive phenotype, measured as a possible change in dyspnea and cough scores from baseline using the L-PF questionnaire in a real-world patient population.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective

The primary objective of this observational study is to investigate the correlation between changes from baseline at 52 weeks in FVC [% pred.] and changes from baseline at 52 weeks in dyspnea score [points] or cough score [points] as measured with the L-PF questionnaire over 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype (excluding IPF):

- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in dyspnea symptom score
- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in cough symptom score

Secondary objectives

- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in dyspnea symptom score
- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in cough symptom score
- Absolute change from baseline in L-PF cough symptom score at week 52
- Absolute change from baseline in L-PF dyspnea symptom score at week 52

Primary and secondary objectives will be analyzed for the treated set.

Additional objectives

Further outcomes will be described in Section 9.3.2.2 of the protocol.

Collection of serious and non-serious adverse drug reactions and fatal adverse effects during the whole NIS (52 weeks) and reporting according to relevant SOP.

This is the first RWE study in patients suffering from chronic fibrosing ILD with a progressive phenotype in Germany being treated with nintedanib. In addition, the German healthcare system is currently strongly supporting all necessary activities to fight the global Covid-19 pandemic with possible effects on the conduct of this study. In order to be able to identify and counteract possible restrictions due to these circumstances, a descriptive snapshot analysis is planned at the time of Last Patient In (LPI) in this study.

9. RESEARCH METHODS

9.1 STUDY DESIGN

Single-arm, open-label observational cohort study according to §4, section 23 and §67, section 6 German Medicines Act (NIS): All included chronic fibrosing ILD with a progressive phenotype patients will receive treatment with nintedanib for approximately 52 weeks. NIS based on newly collected data.

Primarily, this study aims to observe the course of FVC, dyspnea- and cough scores in the L-PF questionnaire over 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype (but not IPF) and investigate possible correlations between

- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in dyspnea symptom score; safety issue: no

- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in cough symptom score; safety issue: no

from each individual patient's difference between baseline and after 52 weeks of treatment with nintedanib. Secondary objectives are change in L-PF cough and dyspnea symptom scores over time.

- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in dyspnea symptom score; safety issue: no

- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in cough symptom score; safety issue: no

- Absolute change from baseline in L-PF cough symptom score at week 52

- Absolute change from baseline in L-PF dyspnea symptom score at week 52

In Germany, more than 99.9 % of citizens are health insured and usually treatment expenses for approved drugs are covered by the health insurance. Therefore, patients receive treatment, except those unwilling to be treated. Those patients are very rare and not suitable as a control group. As Nintedanib is the first treatment approved in Germany in this indication, a comparator arm is not feasible. As treatment is available, a NIS with a placebo group will not get ethical approval in Germany.

Patients recruited for this non interventional study will be treatment-naïve for prior antifibrotic treatment. This will allow to collect clinical baseline data before starting any therapy. After 52 weeks, we will be able to compare these baseline data with the data collected while on nintedanib treatment at the study visits for up to 52 weeks. However, it should be mentioned that due to the natural course of the disease, FVC is expected to decline during the study for the population. As an untreated or placebo group is not planned for due

to ethical reasons, this limitation needs to be considered. However, efficacy and safety of nintedanib have been well established in the RCT INBUILD, also in comparison to placebo. Among others the following will be analyzed:

- comparison of patient data at baseline (patients have no prior antifibrotic treatment) vs data after 52 weeks of nintedanib treatment.

- comparison of the correlation ΔFVC and Δcough/Δdyspnea in the first 26 weeks with vs correlation ΔFVC and Δcough/Δdyspnea in the last 26 weeks.

This approach will allow for comparison between patients untreated and patients after up to 52 weeks of nintedanib treatment as well as during the first and second half year of treatment.

9.2 SETTING

In this NIS, data on the effect of a nintedanib in chronic fibrosing ILD with progressive phenotype in about 100 patients will be collected in routine clinical practice by ca. 20 specialists, experienced in treating ILD patients, (e. g. pulmonologists and rheumatologists) throughout Germany. Each investigator will include ca. 5 consecutive patients for whom the physician had decided on a nintedanib treatment before.

Per definition, non-interventional studies do not include any randomization. In this study, there will be no procedure outside routine clinical practice. Patients will be recruited for this study only after a physician's therapeutic decision to treat the individual patient with nintedanib.

For ethical and/or medical reasons, patients with contraindications (CI) to nintedanib according to SmPC, including pregnant or lactating women, current cancer patients, patients not willing to consent and patients being spouse or lateral relatives to the second degree or economically dependent from the investigator will be excluded.

All calculations for this study, including statistics and patient numbers, are based on the randomized clinical trial INBUILD. In order to be able to duplicate the most crucial design features, in this study nintedanib will solely be tested as a first and only antifibrotic treatment in PF-ILD patients, as it was in INBUILD. Therefore, in accordance with INBUILD trial design, patients must not have used or use any antifibrotic before or during this observational study apart from nintedanib.

This study is planned to observe patients for 12 months. Therefore, patients with a life expectancy of 12 months or less should not be included. As acute exacerbations severely impact life expectancy, patients with acute ILD exacerbations should not be included in the study[12].

Patients must not participate in a parallel interventional clinical trial for not to interfere with the study aims and outcomes.

The impact of excluding those patients seems low, as the number is expected to be minimal and patients with contraindications in any case would not be treated with nintedanib.

9.2.1 Study sites

Data collection of approximately 100 patients from approximately 20 recruiting sites, experienced in treating ILD patients, (e. g., pulmonologists and rheumatologists) throughout Germany is planned. Site selection will be performed to reflect routine care for chronic fibrosing ILD patients with a progressive phenotype in Germany in order to secure representativeness of this specific ILD population.

9.2.2 Study population

Indication
Patients to be recruited within this study have to have a physician diagnosed chronic fibrosing ILD with a progressive phenotype (except IPF), for which nintedanib is an indicated treatment.
Before visit 1, patients must not have been treated with either nintedanib or pirfenidone, i. e., all patients are considered treatment naïve with regard to these antifibrotic treatments.

- Only patients, for whom their treating physician has made the clinical decisions to start nintedanib treatment (but not actually started treatment) independently of this study, are eligible to enter the study.
- During the study, all patients are treated with nintedanib according to standard of care. For each individual patient, a treatment observation period of 52 weeks is aimed for. Handling of patient data with shorter observation period is going to be described in the SAP.

Inclusion criteria
- Adults ≥ 18 years at Visit 1
- Subjects must be contractually capable and mentally able to understand and follow the instructions of the study personnel
- Physician's diagnosis of chronic fibrosing ILD with a progressive phenotype, except IPF
- Treatment with nintedanib in INREAL will be the first and only prescription of any antifibrotic treatment for each individual patient within this observational study after a physician's decision being made for this treatment option earlier
- Outpatients not currently hospitalized with a life expectancy > 12 months per investigator's assessment
- Written informed consent prior to study participation
- Current FVC measurement (taken within the last 3 months) available in the patient file
- Women of childbearing potential must take appropriate precautions against getting pregnant during the intake of nintedanib.

Exclusion criteria

- Patients with contraindications acc. to SmPC
- Prior use of any antifibrotic treatment
- Lack of informed consent
- Pregnant or lactating females
- Any physician diagnosed exacerbation of ILD in the patient's history file, irrespective of time since event
- Current diagnosis of lung cancer
- Respiratory failure (pH < 7,35 and/ or respiratory rate > 30/min) in the patient's history
- Participation in a parallel interventional clinical trial
- Patients being spouse or lateral relatives to the second degree or economically dependent from the investigator

Recently, an ILD incidence rate of 20–30 per 100,000 person-years was suggested for populations across Europe[13].

Suitable patients shall be included consecutively at the sites. Patient selection and proposition of study participation by the investigator will be conducted independently from the treatment decision and after the treatment decision has been agreed between the treating physician and the patient.

If the patient is interested in study participation, the treating physician will explain the study details including the nature and importance of the study and its impact on health and potential risks, both orally and in writing. The patient will have ample time to read the information, ask questions and consider study participation before giving written informed consent.
For more details see sections 9.2.3 (Study Visits) and 10.1. (STUDY APPROVAL, PATIENT INFORMATION AND INFORMED CONSENT).

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

9.2.3 Study visits

In this NIS, data on the effect of a treatment with nintedanib on differences in cough and dyspnea scores, measured via the L-PF questionnaire, will be collected and this information will be assessed in relation to FVC from these patients' medical files in patients with chronic fibrosing ILD with a progressive phenotype.

Four visits are mandatory within this study:

V1 – baseline visit

V3 – mid-observation period
planned visit date: 26 weeks after V1
must not take place earlier than week 20 or later than week 32 after V1

V5 – end of observation
planned visit date: 52 weeks after V1, must not take place earlier than week 46 or later than week 58 after V1

V6 – Follow-up 52 weeks after start of treatment

Each of these visit should take place not earlier than six weeks before and not later than six weeks after the planned visit date (V1 + 26 weeks; V1 + 52 weeks) and thus reflect patients' and physicians' real-world experience.

In addition to Visits 1, 3 and 5 described here, optional study visits will be enabled between V1 and V3 as well as between V3 and V5, each occurring about midway between V1 and V2 or V2 and V3, respectively. Optional visits should take place

optional Visit V2: planned visit date week 13 after V1
if applicable, V2 must not take place earlier than week 7 or later than week 20 after V1

optional visit V4: planned visit date week 39 after V1
if applicable V4 must not take place earlier than week 33 or later than week 45 after V1

When optional visits are conducted, then the same parameters as in Visit 3 should be documented.

Therefore, patients will be seen by their investigator at least every 6 months and up to every quarter of the observational period.

The baseline visit will take the patients ca. one hour including filling out the questionnaires, visits 2 to 6 will take about 30 minutes each. All data documented during those visits, including the questionnaires, record examinations and information necessary during the course of the disease and nintedanib treatment.

If possible, patients who discontinue the study before week 52 for any reason should be contacted for survival status and follow-up data at week 52, as available (Visit 6). A phone contact with the patient / relatives / family doctor is acceptable for V6.

So, the time needed by the patient for the whole study depends on the number of visits performed. The duration of each visit depends on the amount of data to be collected and the possible questions to be discussed between investigator and participant. For baseline, we

presume about one hour, for the following visits about 30 minutes including filling out the questionnaire.

All details on the data collected and tasks performed at each visit are shown in table 9.2.3: 1.

Table 9.2.3: 1 Flow Chart

Parameter	**Visit 1; baseline visit**	**Visit 2; (optional) ca. week 13**	**Visit 3; mid of observa-tion; ca. week 26***	**Visit 4; (optional) ca. week 39**	**Visit 5; end of observa-tion; ca. week 52**	**Visit 6 FU ca. week 52****
Informed Consent	X					
Inclusion / Exclusion Criteria	X					
Patient demographics (age, gender, height, and weight)	X					
Smoking history	X					
History of ILD, including ILD entity and HRCT pattern (where available in patient documentation)	X					
current DLCO measures (where available in patient documentation)	X	X	X	X	X	
Concomitant diseases / Comorbidities	X	X	X	X	X	
Past ILD therapies (6 weeks before visit 1)	X					
Current ILD related or other relevant concomitant medication	X	X	X	X	X	
FVC (mL and % pred.; if available in patient data)	X	X	X	X	X	X
Severity of disease as per the treating physician's estimation (if available in patient data)	X	X	X	X	X	X
L-PF questionnaire, completed by patient	X	X	X	X	X	X

Table 9.2.3: 1 (cont´d) Flow Chart

Parameter	**Visit 1; baseline visit**	**Visit 2; (optional) ca. week 13**	**Visit 3; mid of observa-tion; ca. week 26***	**Visit 4; (optional) ca. week 39**	**Visit 5; end of observa-tion; ca. week 52**	**Visit 6 FU ca. week 52****
Safety: Adverse Drug Reactions (serious and non-serious), fatal AEs, pregnancy	X	X	X	X	X	X
Rationale for treatment discontinuation (if applicable)		X	X	X	X	
Further treatment options yes/no (as applicable		X	X	X	X	X
Intention to continue or discontinue treatment with nintedanib after the study (yes/no)		X	X	X	X	
Survival data						X

* after 26 weeks of observation for each individual patient

** if available and/or patients willing to perform, phone contact acceptable

In addition to the mandatory visits, i.e. Visit 1 (baseline), Visit 3 (mid of observation; 26 weeks after baseline) and Visit 5 (end of observation) and Visit 6 (Follow-up 52 weeks after baseline), optional study visits will be enabled between V1 and V3 (V2) as well as between V3 and V5 (V4), each occurring about midway between V1 and V3 or V3 and V5, respectively. Therefore, patients will be seen by their study investigator at least every 6 months and up to every quarter of the observational period.

When optional visits are conducted, then the same parameters as in Visit 3 should be documented.

Each visit should take place not earlier than six weeks before and no later than six weeks after the planned visit date and thus reflect patients' and physicians' real-world experience.

If possible, patients who discontinue the study before week 52 for any reason should be contacted for survival status and follow-up data to week 52 (visit 6).

For all other patients, visit 5 and visit 6 are completed in the same visit.

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. Emergence of any effectiveness/safety information that could significantly affect continuation of the study

3. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

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

The patients have the right to stop study participation any time and for any reason, without any drawback on their further treatment. Study participation may be stopped for a given patient in case of individual safety issues.

9.3 VARIABLES

The following parameters will be collected and assessed at visits 1 to 5, as applicable:

- Patient demographics (age, gender, height, weight)
- Smoking history, current status (current smokers, former smokers, and never smokers) and pack-years
- History of ILD, including ILD entity and HRCT pattern (where available in patient documentation)
- current DLCO measures (where available in patient documentation)
- Concomitant diseases
- Previous ILD therapies in the 6 weeks before visit 1
- Current ILD related or other relevant concomitant medication
- FVC (mL and % pred.; if available in patient data)
- Severity of disease as per the treating physician's estimation (if available in patient data)
- L-PF questionnaire, completed by patient
- Safety: ADRs (serious and non-serious), fatal AEs, pregnancies during the study
- Rationale for treatment discontinuation (if applicable)
- Intention to continue or discontinue treatment with nintedanib (Ofev®) after the study (yes/no)
- Further treatment options yes/no, as applicable

9.3.1 Exposures

The active ingredient of Ofev® is nintedanib. During this study, it is planned to observe for each patient a treatment period with nintedanib of approximately 52 weeks.

The recommended daily dose of nintedanib (Ofev®) is 150 mg twice daily administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used in patients who do not tolerate the 150 mg twice daily dose.
The treating physician ensures that the treatment follows all specific requirements described in the SmPC as e.g. contraindications including pregnancy, monitoring, discontinuation, dose reduction etc.

The Summaries of Product Characteristics on Ofev® is contained in the NIS ISF in the "Summary of Product Characteristics" section.
Note: The recommended doses stated in the Summary of Product Characteristics should not be exceeded.

Other adequate therapy will be applied according to label as described in the respective SmPCs.

The study aims to observe for each patient a treatment period with nintedanib of approximately 52 weeks (including a mid-of-observation evaluation and 2 further optional intermediate visits). As there is no untreated comparator group, each patient included in the study is planned to be continually exposed to nintedanib as a standard of care for the whole observational period of 52 weeks at the indicated dosage of 150 mg daily. As this is a real-world observational study, patients will be instructed on the correct drug application by their treating physician. In case of dose reductions deemed necessary by the treating physicians, these may be applied according the SmPC. All cases of dose reduction or dose interruption will have to be documented and reasons given in the eCRF.

A dose interruption of nintedanib for more than 12 weeks and/or initiation of another antifibrotic therapy during the observation phase of the study will result in exclusion of the concerned patients' data from efficacy analysis.

Handling of missing data will be described in the SAP.

Exposure variables will be cough score and symptoms score as measured via L-PF questionnaire.
The complete L-PF questionnaire will be collected by the site in an eCRF. Each question is answered by the patient indicating one tick-box answer per question. Only one statement can be chosen. The higher the score the greater the impairment.

Ofev® (Nintedanib) is authorized in Germany for the treatment of adult patients suffering from chronic fibrosing ILD with a progressive phenotype as Ofev®. Each patient in need and meeting the criteria defined in the SmPC may get an Ofev® prescription by the treating physician. Statutory health insurances in Germany cover Ofev® prescription costs.

Furthermore, Ofev® is also indicated to treat adults with idiopathic pulmonary fibrosis (IPF), systemic sclerosis associated interstitial lung disease (SSc-ILD), and other chronic fibrosing interstitial lung diseases which are progressive.

This study aims to continually observe adult patients suffering from chronic fibrosing ILD with a progressive phenotype who are newly treated with nintedanib without any previous antifibrotic therapy, i. e. neither pirfenidone nor nintedanib, for 52 weeks. Neither switchers nor past or current users of nintedanib (or pirfenidone) are to be included. Based on the INBUILD study, this study is planned in a parallel way. It is assumed that PROs will be determinable best in new users. All calculations for this study, including statistics and patient numbers, are based on the randomized clinical trial INBUILD. In order to be able to duplicate the most crucial design features, in this study nintedanib will solely be tested as a first and only antifibrotic treatment in PF-ILD patients, as it was in INBUILD. Therefore, in accordance with INBUILD trial design, patients must not have used or use any other antifibrotic before or during this observational study, except nintedanib during the study.

9.3.2 Objectives and Outcomes

The primary objective of this study is to investigate the correlation between changes from baseline to 52 weeks in FVC [% pred.] and changes from baseline to 52 weeks in dyspnea score [points] or cough score [points] as measured with the L-PF questionnaire over 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype (excluding IPF):

- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in dyspnea symptom score

- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in cough symptom score

from each individual patient's difference between baseline and after 52 weeks of treatment with nintedanib. As such, comparisons will be made within treated population alone.
The questionnaire will be completed by the patient during each visit and will reflect the actual symptoms and the patient's status at that day, as described by the patient.

There will be no true comparison group of untreated patients in this study for a complete interpretation of findings since all patients in this study will receive nintedanib after their treating physician had decided for this therapeutic option for the respective individual patient.

Therefore, an untreated patient population will not exist. Further, the within-group comparison among treated patients before and after nintedanib initiation may not be ideal due to the process of progression itself during the follow up period which may limit the comparability of the two time-points.

9.3.2.1 Primary outcomes

- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in dyspnea symptom score
- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in cough symptom score

The primary outcomes do not touch any safety question.

9.3.2.2 Secondary outcomes

- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in dyspnea symptom score; safety issue: no
- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in cough symptom score; safety issue: no
- Absolute change from baseline in L-PF cough symptom score [points] at week 52; safety issue: no
- Absolute change from baseline in L-PF dyspnea symptom score [points] at week 52; safety issue: no

Primary and secondary outcomes will be analyzed for the Treated Set.

The secondary outcomes do not touch any safety question.

9.3.3 Covariates

Covariates for adjustment will include patient demographics and disease characteristics. These will be discussed in the SAP.

9.4 DATA SOURCES

Medical records collected through routine clinical care will be used to assess the inclusion/exclusion criteria of patients as well as for patient demographics, smoking history, collection of previous ILD medication, concomitant diseases, and concomitant medication, as well as for the health data of the patient during the course of the observation.

The LPF questionnaire will be provided as paper version to the patient to be filled out in writing at visits V1 to V5, as applicable.

All patients will be enrolled consecutively.

9.5 STUDY SIZE

In the INBUILD trial, patient groups on placebo vs nintedanib therapy differed in both their loss of FVC and dyspnea and cough symptom scores in the L-PF questionnaire (Figure 9.5:1; see below).

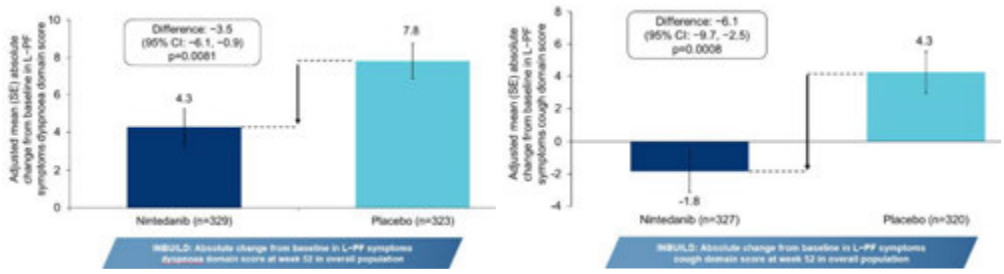

Figure 9.5:1 Changes from baseline to week 52 in L-PF symptoms dyspnea (left) and cough (right), domain scores respectively, seen in INBUILD

ΔFVC, Δdyspnea and Δcough symptom scores from INBUILD (see Table 9.5:1 below) were applied to estimate sample sizes.

Correlations between the change from baseline to week 52 in FVC (both FVC in mL and FVC as % predicted) and the change from baseline to week 52 in both L-PF dyspnea symptom score and cough symptom score measured by Pearson's correlation coefficient were $\rho \approx -0.3$ in the Nintedanib arm of the treated set (see Table 9.5:1 below).[14]

Table 9.5:1 Pearson correlation between the change from baseline to week 52 in FVC and the change from baseline to week 52 in L-PF symptoms scores in the Nintedanib arm (results were similar for the total population.)

Pearson correlation (change from baseline at week 52) between FVC and L-PF symptoms	Coefficient	95% Confidence interval	
		Lower	Upper
L-PF symptoms dyspnoe score and …			
FVC in ml	-0.35	-0.45	-0.23
FVC (% predicted)	-0.37	-0.47	-0.26
L-PF symptoms cough score and …			
FVC in ml	-0.26	-0.37	-0.14
FVC (% predicted)	-0.26	-0.37	-0.14

Currently, a meaningful threshold ("MCID") has been published for neither the cough nor the dyspnea domain of the L-PF. However, should that information become available during the study, study results will be discussed in relation to meaningful thresholds ("MCID") values.

Given a correlation ρ between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in dyspnea symptom score as well as change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in cough symptom score of approximately -0.3, then 84 patient data sets would be required for evaluation. Assuming an estimated drop-out rate of approx. 15 % 100 patients will have to be recruited for this study. With this patient number (N = 84) and the assumption of a Pearson correlation of -0.3, the overall type I error is protected at the two-sided 0.05 level with a power of 80 %.

Therefore 100 patients are planned to be recruited for this NIS by about 20 specialists, experienced in treating ILD patients, (e. g., pulmonologists and rheumatologists) throughout Germany. Each investigator will include ca. 5 consecutive patients for whom the physician had decided for a treatment with nintedanib before actual recruitment of the patient. The treatment decision will have to have taken place before actual recruitment of the patient.

Due to the observational nature of the study, all analyses are exploratory. No weighting will be applied to either of the co-primary endpoints. All analyses in this observational study are exploratory. No weighting will be applied to either of the co-primary endpoints.

9.6 DATA MANAGEMENT

The data management plan is summarized below. Full details of the data management plan are documented in a separate NIS-Data Management and Review Plan (NIS-DMRP).

The NIS-DMRP will 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. Source data verification (SDV) will be performed at each recruiting site and further at sites identified by a risk-based approach as needed.

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 and the safety requirements of the FDA (US Food & Drug Administration) concerning systems for the data acquisition of clinical studies in accordance with "Title 21 Code of Federal Regulations (21 CFR Part 11): Electronic Records; Electronic Signatures. Patient confidentiality will be strictly maintained.

9.6.1 Data Entry / EDC

Data entry into the eCRF including the data of the patient questionnaires follows the instructions in the EDC system user manual and is further supported by help and hint texts. Support documents will also be provided within the online system documents, which give explanations to basic functions and field types in the eCRF.
With data entry into the EDC system, all changes and user information will be saved in an audit trail.
The data review and validation steps for a project are defined in the data validation plan (DVP).

The DVP includes all definitions of electronic checks and the defined manual checks, which will be performed directly in the EDC system or can be based on listings.
Electronic edit checks (eChecks) are performed automatically and directly when entering data into the eCRF. Missing or implausible data entries or are indicated to the user immediately. Manual Checks are applied to verify the entered data validity and plausibility.

Queries can result from various sources:

- Manual Checks by data management
- Manual Checks by pharmacovigilance
- Source data verification during on-site monitoring

9.6.2 Source Documents

The source documents are contained in the patient’s medical record. The filled-in patient questionnaires are regarded source data and must be kept in the study site file. Data collected on the eCRFs must be traceable to these source documents in the patient’s medical records as far as this is routine documentation. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Sponsor before any destruction of medical records of study participants.

9.6.3 File Retention and Archiving

The study database and all study-specific documents received by [redacted] will be transferred to BI regularly during and after the study period. Archiving will be performed by BI Pharma in accordance with BI SOPs.

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the investigator agrees to keep records, including the identity of participating patients, copies of all CRFs, SAE forms, source documents and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation that contains all documents necessary for the conduct of the study and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least thirty years after the completing participation in the study. In the event that archiving of the file is no longer possible at the site, the site will be instructed to notify the Sponsor.

9.7 DATA ANALYSIS

The statistical analysis plan for the study is summarized below. Full details of the statistical analysis will be documented in the SAP, which will be finalized before the end of data collection.

All patients who have received at least one dose of nintedanib will be included in the treated set. All analyses will be performed on the treated set.

9.7.1 Main analysis

For the analysis of the primary outcomes

- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in dyspnea symptom score
- Correlation between change from baseline to week 52 in FVC [% pred.] and change from baseline to week 52 in cough symptom score

Pearson measures of correlation along with 95% two-sided confidence intervals and the two-sided p-values will be provided.

For the secondary outcomes

- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in dyspnea symptom score
- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in cough symptom score

Pearson measures of correlation along with 95% two-sided confidence intervals and the two-sided p-values will be provided.

The secondary outcomes

- absolute change from baseline in L-PF symptoms dyspnoea domain score between week 52 and baseline
- absolute change from baseline in L-PF symptoms cough domain score between week 52 and baseline

will be analyzed using a restricted maximum likelihood (REML) based repeated measures approach. Analyses will include the fixed, categorical effect of visit, as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. An unstructured (co)variance structure will be used to model the within-patient measurements.

9.7.3 Safety Analysis

All adverse drug reactions (ADRs) (serious and non-serious) and all AEs with fatal outcome as collected per study protocol will be included and summarised in the final study report.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Kaplan-Meier plots will be produced for the time to premature treatment discontinuation, for the time to first dose reduction and for the time to first treatment interruption.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The residual effect period is defined as the 28 days after the date of the last dose of study medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered ‘treatment-emergent’.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA.

9.8 QUALITY CONTROL

The quality control, review, and monitoring plan are summarized below. The NIS-DMRP details the data management plans, including quality review measures, site monitoring plans, and site qualification/training plan.

All participating sites will receive a comprehensive study site file with all information on the NIS. Site staff will be further trained by a mandatory webinar. Training will be documented in the study site file.

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.

To provide further quality assurance of the documented patient observations, source data validation will take place at each recruiting site and involve an on-site review of the documented data for completeness and consistency by a monitoring visit. An additional check/ review of the quality assurance of this NIS can be performed. Depending on site recruitment and data status in the eCRF, monitoring visits will be planned following a pre-defined risk analysis with risk-based approach. Details will be specified in the study monitoring plan. In case of decreasing compliance (i.e. of missing data, data discrepancies, protocol violations, etc.) a for-cause audit or risk-based monitoring visits will be performed. At study end, the database and all relevant programs as e.g. statistical programming will be transferred to BDS to be archived in the appropriate DMS.

9.9 LIMITATIONS OF THE RESEARCH METHODS

This study aims to continually observe adult patients suffering from chronic fibrosing ILD with a progressive phenotype who are newly treated with nintedanib without any previous antifibrotic therapy, i. e. neither pirfenidone nor nintedanib, for 52 weeks.

A NIS appears the most suitable instrument for obtaining information about the use of medicines in everyday therapeutic practice and thus for investigating prospectively questions in everyday therapeutic 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. The choice of treatment is at the discretion of the investigator.

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 centers with access to all available and approved treatment options in that country for the targeted patient population. 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. Furthermore, baseline characteristics will be compared with INBUILD data to explore possible bias.

9.9.1 Data quality assurance

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

9.9.2 Study records

Electronic Case Report Forms (eCRFs) for individual patients will be provided by the sponsor, via remote data capture.

9.9.2.1 Source documents

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

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

For eCRFs, all data must be derived from source documents.

9.9.2.2 Direct access to source data and documents

The investigator/institution will permit study-related monitoring, audits, 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)). BI study staff 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 9.9.2.1.

9.9.3 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 the current version, Guidelines for Good Pharmacoepidemiology Practice (GPP), and the relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

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

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

This NIS 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: Ethikkommission der Medizinischen Fakultät Heidelberg) 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) per GPP and according to the regulatory and legal requirements of the participating country.

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

The patients' study participation is voluntary and the patients have the right to stop study participation any time and for any reason, without any drawback on their further treatment. If patients withdraw, they will decide if their study data are to be deleted or may be further used for the analysis of the study. If the patients agree, survival data after 52 weeks will be collected also from patients who withdraw from study participation.
These decisions may be revised by the patient during the course of the study and the deletion of the study data may be requested.

Once the data are anonymized and analysed, data deletion upon patient wish is not possible any more.

10.2 STATEMENT OF CONFIDENTIALITY

Federal and local legal requirements concerning confidential medical communication as patient names and other confidential information and concerning data protection (DSGVO, BDSG, LDSG) as well as medical professional privilege will be followed.

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. The medical and personal patient data may be inspected by dedicated study site staff and by dedicated monitors (CRAs) for quality assurance reasons. All this personnel is obligated to confidentiality.
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.

During the study, medical results and reports and personal information from the patients will be collected in patient files at the study sites. Those data important for the study will be collected pseudonymisedly via an electronic case report form and accumulated in a study database. The pseudonymisation key is kept confidential by the investigator at the study site. Before analysis, the data will be anonymized and the reports from this analysis will be provided to the sponsor of the study, Boehringer Ingelheim. After analysis and finalization of the study report, the anonymized data will be transferred to Boehringer Ingelheim.
The medical and personal patient data may be inspected by dedicated study site staff, by authorized dedicated monitors (CRAs) for quality checks and by health authority staff in case of an inspection. For those quality checks and authority inspection the patient releases the treating physician from the medical professional privilege.

Study data will be kept for 30 years and then be destroyed.

10.3 BENEFIT-RISK ASSESSMENT

The benefit to gain with this study will be reliable and evidence based information about a possible correlation of changes in patient reported outcomes (PRO) as cough and dyspnea to physical changes due to the course of the disease as shown in FVC. This might turn out to be a helpful early clinical sign of disease progression, easily to be noticed by the patient and to be reported – solicited or unsolicited – to the treating physician. Furthermore, this may help to further establish this PRO as a tool in clinical practice and improve monitoring of the patients.

Additionally, the medical community will get more and deeper knowledge of the severe lung disease PF-ILD and its treatment with nintedanib. Patients do not personally benefit from participating in this NIS while being treated, but they contribute to gaining better insight into the disease and thus to potential improvement of treatment options in the future.

The risks and strains for the patient caused by participating in this NIS are marginal. They will follow routine treatment and regular follow-up for their disease and the questionnaire is the only study-related task. There is no additional risk by study participation.

10.4 INFLUENCE OF COVID- 19 PANDEMIC ON THE STUDY PARTICIPANTS

All patients to be included into this NIS suffer from a severe medical condition and are in need of treatment according to their treating physician's assessment. The patients will be treated in usual care, all data documented during those visits, including the questionnaires, record examinations and information necessary during the course of the disease and nintedanib treatment. No additional visits or examinations are demanded or required other than in clinical routine. So there is no additional risk for the patients in the COVID-19 pandemic caused by the study apart from their inherent risk as patients with a serious systemic disease affecting the lung.

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 drug reaction
An adverse drug reaction (ADR) 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.

Adverse events relating to gastrointestinal perforation and hepatic injury will be considered as AESIs.

Signs of hepatic injury are defined as:

- ALT and/or AST ⩾8 fold ULN
- ALT and/or AST ⩾3 fold ULN and total bilirubin ⩾ 2 fold ULN in the same blood draw sample

These lab findings constitute a hepatic injury alert and any patient showing these lab abnormalities needs to be followed up according to the drug-induced liver injury (DILI) checklist.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed. Should the results meet the criteria of hepatic injury, the procedures described in the DILI checklist should be followed.

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 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.

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria version 5.0 (2017) in the (e)CRF.

Pregnancy:

In rare cases, pregnancy might occur in a NIS. Once a patient has been enrolled in the study and has taken study medication, the investigator must report any drug exposure during pregnancy in a study participant within 7 days by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form (Part B).

The ISF will contain the Pregnancy Monitoring Form (Part A and B). As pregnancy itself is not to be reported as an AE, in the absence of an accompanying serious ADR and/or AESI, only the Pregnancy Monitoring Form and not the NIS AE form is to be completed. If there is a serious ADR and/or AESI associated with the pregnancy a NIS AE form must be completed in addition.

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

All ADRs and AESIs, 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.

Expedited Reporting of AEs and Drug Exposure during Pregnancy to BI Pharmacovigilance

The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form from signing the informed consent onwards until the end of the study and provide o BI unique entry point:

All **serious ADRs** associated with the studied medical product nintedanib	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to *studied medical product* nintedanib	immediately within 24 hours
All **protocol specified AESIs**	Immediately within 24 hours
All **non-serious ADRs** associated with the studied medical product nintedanib	7 calendar days
Drug exposure during pregnancy	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 page and the NIS AE form.

11.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Results of this non-interventional study will be disclosed on encepp.eu and clinicaltrials.gov and a study specific publication plan will be developed to describe planned publications.

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

[1] Boehringer Ingelheim. Rosenstock B. CTP for Trial No. 1199.247; Document No. c03736471-02
[2] Cottin V et al. Eur Repir Rev 2018;27:180076
[3] Richeldi L et al. N. Engl. J. Med., 365 (2011), pp. 1079-1087
[4] Richeldi L et al. N. Engl. J. Med., 370 (2014), pp. 2071-2082
[5] Rivera-Ortega P et al. Ther Adv Respir Dis 2018;12:1753466618800618
[6] Crestani B et al. Lancet Respir Med. 2019;7(1):60-68.
[7] Flaherty KR et al. N Engl J Med 2019;381:1718-27
[8] Swigris JJ et al.; INBUILD Trial Investigators. ATS 2020, 116th Int Conf of the American Thoracic Society (ATS), Philadelphia, 15 - 20 May 2020. Am J Respir Crit Care Med 2020 ; 201; A2754
[9] Swigris JJ et al. Eur Respir Rev. 2018;27(150):180075
[10] BI Clinical Trial Report; BI trial number 1199.247
[11] Boehringer Ingelheim. Rosenstock B. CTP for Trial No. 1199.247; Document No. c03736471-02
[12] Salonen J et al. BMJ Open Respir Res. 2020.
[13] Kreuter M et al. Biomed Res Int. 2015;2015:123876.
[14] BI Clinical Trial Report; BI trial number 1199.247

13.2 UNPUBLISHED REFERENCES

Not applicable

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

The study has already been accepted by ENCEPP.

Von: [redacted]
An:
Betreff: WG: Your study registration with EU PAS Register Reference: EUPAS38272 has been accepted
Datum: Donnerstag, 26. November 2020 14:52:10

-----Ursprüngliche Nachricht-----
Von: EU_PAS_Register@ema.europa.eu <EU_PAS_Register@ema.europa.eu>
Gesendet: Mittwoch, 25. November 2020 10:28
An: [redacted]
Cc: EU_PAS_Register@ema.europa.eu
Betreff: Your study registration with EU PAS Register Reference: EUPAS38272 has been accepted

CAUTION! Please do not click links or open attachments unless you recognize the sender, this email is from an External Sender (outside Boehringer-Ingelheim)

Dear [redacted]

Thank you for submitting your application to register your study with the EU PAS Register. We are pleased to inform you that your application has been accepted and that the information on your study has been entered in the EU PAS Register which is accessible to the public.

You may login with your username and password to update your details at any time.

Your username is: [redacted]
Your password is: xxxxxxxxxxxxxx

For further information or queries, please do not hesitate to contact us at
mailto:eu_pas_register@ema.europa.eu

We look forward to working with you.

Kind regards,
EU PAS Register

This e-mail has been scanned for all known viruses by European Medicines Agency.

ANNEX 3. ADDITIONAL INFORMATION

Not applicable

ANNEX 4. REVIEWERS AND APPROVAL SIGNATURES

Not applicable

Signatures will be provided electronically via approval workflow in the DMS for submission documents.

APPROVAL / SIGNATURE PAGE

Document Number: c34369089 **Technical Version Number:2.0**

Document Name: nis-protocol-1199-0449

Title: Prospective observational investigation of possible correlations between change in FVC and change in cough or dyspnea scores using the living with pulmonary fibrosis questionnaire (L-PF) between baseline and after approximately 52 weeks of nintedanib treatment in patients suffering from chronic fibrosing ILD with a progressive phenotype

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Clinical Trial Leader	[redacted]	08 Feb 2021 12:58 CET
Approval-Project Statistician		08 Feb 2021 13:05 CET
Approval-[redacted] Safety Evaluation Therapeutic Area		08 Feb 2021 14:10 CET
Approval-[redacted] Medical Affairs		08 Feb 2021 14:58 CET
Approval-Team Member Medical Affairs		08 Feb 2021 17:38 CET
Approval-Other		11 Feb 2021 01:58 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed