Boehringer Ingelheim

Non-Interventional Study (NIS) SEAP

Document Number:	NA
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 –** Nintedanib 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
SEAP version identifier:	3.0
Date of last version of SEAP:	17 Nov 2022
NIS Statistician [SEAP author]	[redacted] Phone: [redacted] Fax: [redacted] [redacted]
NIS [redacted] [SEAP reviewer]	[redacted] phone: [redacted] [redacted]
Oversight Data [redacted] [SEAP reviewer]	[redacted] phone: [redacted] [redacted]

1. TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
BI	Boehringer Ingelheim
CI	Confidence interval
Covid-19	Coronavirus disease 2019
CRF	Case report form
DLCO	Diffusing capacity of the lungs for carbon monoxide
FVC	Forced vital capacity
HRCT	High-resolution computer tomography
ICH	International conference on harmonisation
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
IQR	Interquartile range
L-PF	Living with pulmonary fibrosis questionnaire
LPI	Last patient in
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed effect Model for Repeated Measures
NIS	Non-interventional study
PF-ILD	Progressive fibrosing interstitial lung disease
PPS	Per protocol set
PRO	Patient-reported outcome
PT	MedDRA preferred term
RCT	Randomized controlled trial
REML	Restricted maximum likelihood
RWE	Real-world evidence
RWE CoE	Real-world evidence analytics centre of excellence
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SEAP	Statistical and epidemiological analysis plan
SmPC	Summary of product characteristics
SOC	MedDRA system organ class
SOP	Standard operating procedure
TDM	Trial Data Manager
TEAE	Treatment-emergent adverse event
TLF	Table, list and figures
TM Epi	Team Member Epidemiology
TS	Treated set
TSTAT	Trial statistician

2. RESPONSIBLE PARTIES

NIS Statistician [SEAP author]
- [redacted] (Statistician)

SEAP reviewers are:

- BI NIS [redacted] [SEAP reviewer]
  - [redacted] (NIS [redacted])
- Oversight BI TDM [SEAP reviewer]
  - [redacted]
- RWE CoE [SEAP reviewer]
  - [redacted]
- TSTAT
  - [redacted]
- TM Epi [SEAP reviewer]
  - [redacted]

3. PURPOSE AND SCOPE

As per ICH E9 [1] (International Conference on Harmonisation), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Statistical and Epidemiological Analysis Plan (SEAP) assumes familiarity with the Observational plan, including Protocol Amendments. In particular, the SEAP is based on the planned analysis specification as written in Observational plan Section 9.7 “Data Analysis”. Therefore, SEAP readers may consult the Observational plan for more background information on the study, e.g., on study objectives, study design and population, definition of measurements and variables, planning of sample size, randomization.

SAS® Version 9.4 (or later version) will be used for all standard analyses.

4. AMENDMENTS AND UPDATES

This amendment encompasses changes related to the analysis populations.

Patients in the treated set needed to sign the written informed consent form. The analysis on the per protocol set was not required in the observational plan and was added post hoc in order to identify a treatment effect which would occur under optimal conditions. Patients in the per protocol set needed to meet all inclusion and exclusion criteria and must not have violated any important protocol deviations.

5. RESEARCH QUESTION AND OBJECTIVE

5.1 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

5.2 SECONDARY OBJECTIVE

- 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.

5.3 ADDITIONAL OBJECTIVE

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.

6. RESEARCH METHODS

6.1 STUDY DESIGN

This is a 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.

For more details on study design please see section 9.1 of the Study Protocol.

6.2 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 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.

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.

6.3 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. Patient's data with shorter observation period will be analyzed up to the date of data collection of the corresponding patient.

Inclusion and exclusion criteria are listed in section 9.2.2 of the Study Protocol as of 8 FEB 2021. Exclusion criterion 4 was changed in Local Amendment 1.0 dated 20 JAN 2022.

6.4 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. In addition to Visits 1, 3 and 5 optional study visits will be enabled. Each of these visits should take place not earlier than six weeks before and not later than six weeks after the planned visit date:

V1 – baseline visit

V3 – 26 weeks after V1 (20 – 32 weeks)

V5/V6 – 52 weeks after V1 (46 – 58 weeks)

Optional visits should take place:

V2 – 13 weeks after V1 (7 – 20 weeks)

V4 – 39 weeks after V1 (33 – 45 weeks)

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).

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.

For more details on study visits please see section 9.2.3 of the Study Protocol.

7. 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

Living with pulmonary fibrosis questionnaire (L-PF)

The complete L-PF questionnaire is a 44 item questionnaire with two modules:

1) symptoms (23 items)

2) impacts (21 items)

The symptom module consists of three subdomains a) dyspnea b) cough c) fatigue. The impacts module yields a single impacts score. Symptoms and impacts scores are summed to yield a total L-PF score. The total and domain L-PF scores range from 0 to 100, the higher the score, the greater the impairment.

Scoring is performed as a summary score, the mean of the dimension ratings multiplied by 100. If the missing items are $\geqslant$ 50 % within a score, then the corresponding score is set to missing. Each question is answered by the patient indicating one tick-box answer per question. Only one statement can be chosen.

Scoring of L-PF questionnaire [2]

Module	Domain	Scoring
Symptoms	Dyspnea items 1-12	*Items 1, 2, 4-10 and 12* If 'Yes' is ticked, scores range from 0 to 4. If 'No' is ticked and A* is ticked, the score is 5. If 'No' is ticked and B** is ticked, the item is not scored and does not contribute to the denominator. If 'No' is ticked and neither A or B is ticked, the item is counted as missing but the item does contribute to the denominator. *Items 3, 11* Scores 0 to 4 Dyspnea Symptom Score = $\frac{sum\ of\ items\ 1-12}{total\ score\ possible\ for\ items}$ x 100
	Cough items 13-18	Scores range from 0 to 4 for each item. Cough Symptom Score = $\frac{sum\ of\ items\ 13-18}{24}$ x 100
	Energy items 19-23	*Items 19-23* Scores range from 0 to 4 for each item. *Item 23* If 'Yes' is ticked, scores range from 0 to 4. If 'No' is ticked, the item is not scored and does not contribute to the denominator. Energy Symptom Score = $\frac{\text{sum of items } 19-23}{\text{total score possible for items (20 or 16)}}$ x 100
Impact	Dyspnea items 1-6	Scores range from 0 to 4 for each item. Dyspnea Impact Score = $\frac{\text{sum of items } 1-6}{24}$ x 100
	Cough items 7-11	Scores range from 0 to 4 for each item. Cough Impact Score = $\frac{\text{sum of items } 7-11}{20}$ x 100
	Energy items 13-14	Scores range from 0 to 4 for each item. Energy Impact Score = $\frac{\text{sum of items } 13-14}{8}$ x 100
	Global items 12, 15-21	Scores range from 0 to 4 for each item. Global Impact Score = $\frac{\text{sum of items 12 and } 15-21}{32}$ x 100

* Answer A: Patient avoided the activity because it was too difficult.
** Answer B: Does not apply because the patient did not want to or had no opportunity to do the activity.

Symptoms Total Score = $\frac{sum\ of\ Dyspnea\ Symptom,Cough\ Symptom,Energy\ Symptom}{3}$

Impacts Total Score = $\frac{sum\ of\ Dyspnea\ Impact,Cough\ Impact,Energy\ Impact,Global\ Impact}{4}$

Total L-PF Score = $\frac{sum\ of\ Symptoms\ Total\ and\ Impacts\ Total}{2}$

Overall survival (OS): Overall survival of a patient is defined as the time from first dose of nintedanib until date of death. OS for patients who did not die will be censored at the date of last contact.

Time to premature treatment discontinuation: Time to premature treatment discontinuation is defined as the time from first dose of nintedanib until date of premature treatment discontinuation of nintedanib. The calculated time for patients without premature treatment discontinuation of nintedanib will be censored at the date of last contact.

Time to first dose reduction: Time to first dose reduction is defined as the time from first dose of nintedanib until the start date of first dose reduction to 100 mg/ twice daily or to other dose/ frequency excluding treatment interruption with 0 mg nintedanib administration daily. The calculated time for patients without dose reduction of nintedanib will be censored at the date of last contact.

Time to first treatment interruption: Time to first treatment interruption is defined as the time from first dose of nintedanib until the start date of first treatment interruption with 0 mg nintedanib administration daily. The calculated time for patients without treatment interruption of nintedanib will be censored at the date of last contact.

Treatment-emergent adverse events (TEAE): 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 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'.

Change from baseline to week 52 in FVC [% pred.]: FVC [% pred.] at week 52 – FVC [% pred.] at baseline

Change from baseline to week 52 in FVC [mL]: FVC [mL] at week 52 – FVC [mL] at baseline

Change from baseline to week 52 in L-PF dyspnea symptom score: L-PF dyspnea symptom score at week 52 – L-PF dyspnea symptom score at baseline

Change from baseline to week 52 in L-PF cough symptom score: L-PF cough symptom score at week 52 – L-PF cough symptom score at baseline

7.1 Exposures

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 twice daily. As this is a real-world observational study, patients will be instructed on the correct drug application by their treating physician. 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.

Exposure variables will be cough score and symptoms score as measured via L-PF questionnaire.

7.2 Outcomes

7.2.1 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

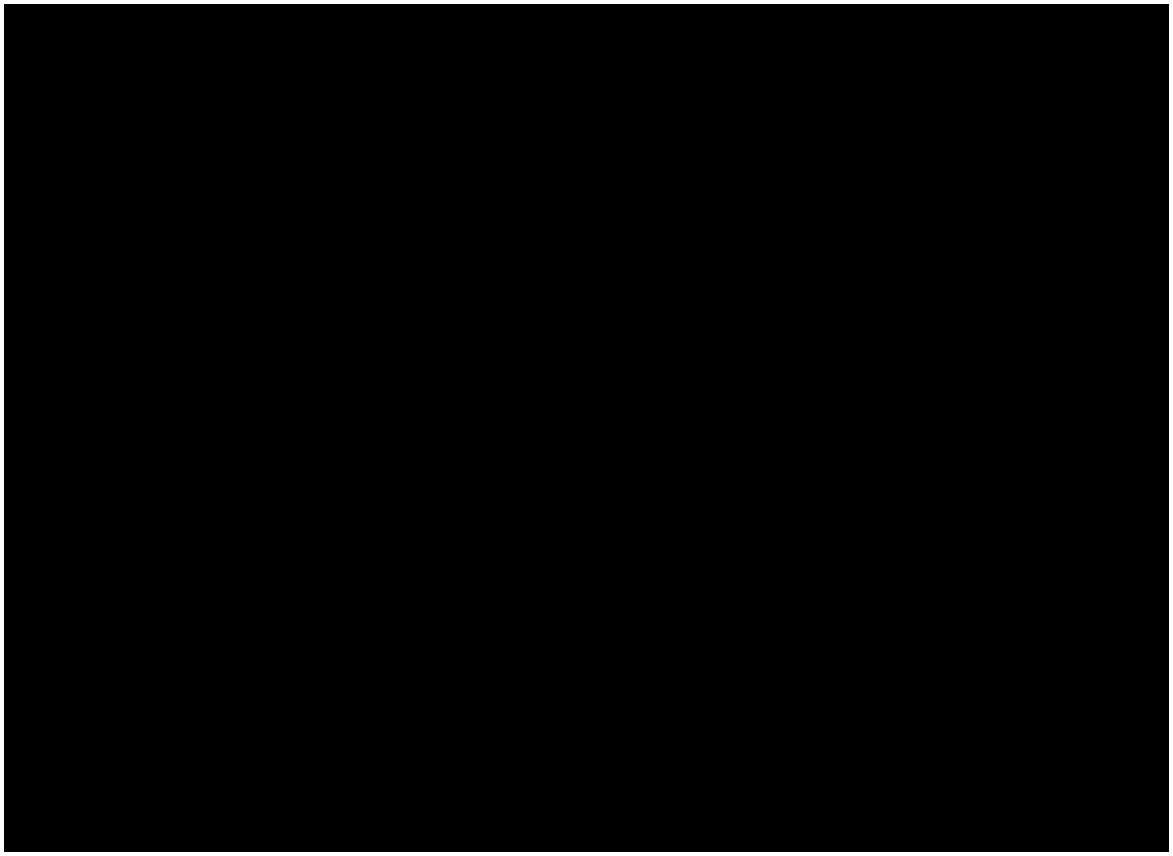
The primary outcomes do not touch any safety question.

7.2.2 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.



[redacted]

7.3 Covariates

Covariates for adjustment will include the following disease characteristics:

- Pulmonary function test (DLCO) result [% pred] at baseline
- FVC result [% pred.] at baseline
- FVC result [mL] at baseline

8. 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 L-PF questionnaire will be provided as paper version to the patient to be filled out in writing at visits V1 to V5, as applicable.

No further data sources are needed for statistical analysis.

9. DATA MANAGEMENT AND SOFTWARE/TOOLS

9.1 Software/Tools

SAS® Version 9.4 or higher will be used for all analyses.

9.2 Handling of Missing Values

All patient discontinuations will be documented and the reason for discontinuation will be recorded.
In general, it is not planned to impute missing values. Exceptions are detailed in the subsequent subsections.

9.2.1 Change from baseline endpoints

The statistical Mixed effect Model for Repeated Measures (MMRM) used for the analysis of continuous secondary endpoints allows for form-level missing data, assuming they are missing at random. Item-level data for the PRO measures will be handled according to the instructions provided by the instrument developer.

9.2.2 L-PF

The L-PF scores represent means. Missing items are generally not counted in the denominator. Please note the following exception for the Dyspnea score items 1, 2, 4 – 10 and 12:

- If "No" is ticked and neither "A*" nor "B**" is ticked, the item is counted as missing but the item does contribute to the denominator.
- If "No" is ticked and "B" is ticked, then the item is not scored and does not contribute to the denominator.

[*] Answer A: Patient avoided the activity because it was too difficult.
[**] Answer B: Does not apply because the patient did not want to or had no opportunity to do the activity.

If the missing items are ⩾50% within a score, then the corresponding score is set to missing.

9.3 Handling of Inconsistencies in Data and Outliers

Not planned.

10. DATA ANALYSIS

Treated Set (TS): All patients with signed informed consent who received at least one dose of nintedanib will be included in the treated set.

Per Protocol Set (PPS): All patients from the treated set who met all inclusion and exclusion criteria and did not violate any important protocol deviations.

Important protocol deviations:

- Dose interruption of nintedanib for more than 12 weeks and/or initiation of another antifibrotic therapy during the observation phase of the study.
- Missing patient questionnaires or other variables necessary for assessment of the primary study outcome
- Last patient visit completely missing (if no data is available for week 52)
- No FVC measurement available within 3 months prior to inclusion and FVC was not evaluated at baseline

All analyses will be performed on the treated set. Primary and secondary outcomes will be analysed for patients who have available data for the analysis of the efficacy endpoints. Additionally, all analyses for baseline and efficacy will be done on the per protocol set if ⩾ 10% of the treated set is omitted.

All analyses on the treated and per protocol set will be performed using the method of time windowing: Only data will be used that was documented at performed visits within ± 6 weeks of the planned visit date (see 6.4 STUDY VISITS). For purpose of sensitivity primary and secondary endpoints will also be analysed without time windowing.

No subgroup analyses are planned due to the small number of patients.

For categorical variables summary tabulations of the number and percentage (%) relative to the treated set (unless otherwise specified, all patients in the patient set whether they have non-missing values or not) within each category of the parameter will be presented. The category missing will be displayed only if there are actually missing values.

For continuous variables number of values, mean, standard deviation, minimum, 25th percentile, median 75th percentile, maximum and number of missing values will be presented.

Percentages will be rounded to two decimal places.

No interim analysis is planned.

10.1 Main analysis

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

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

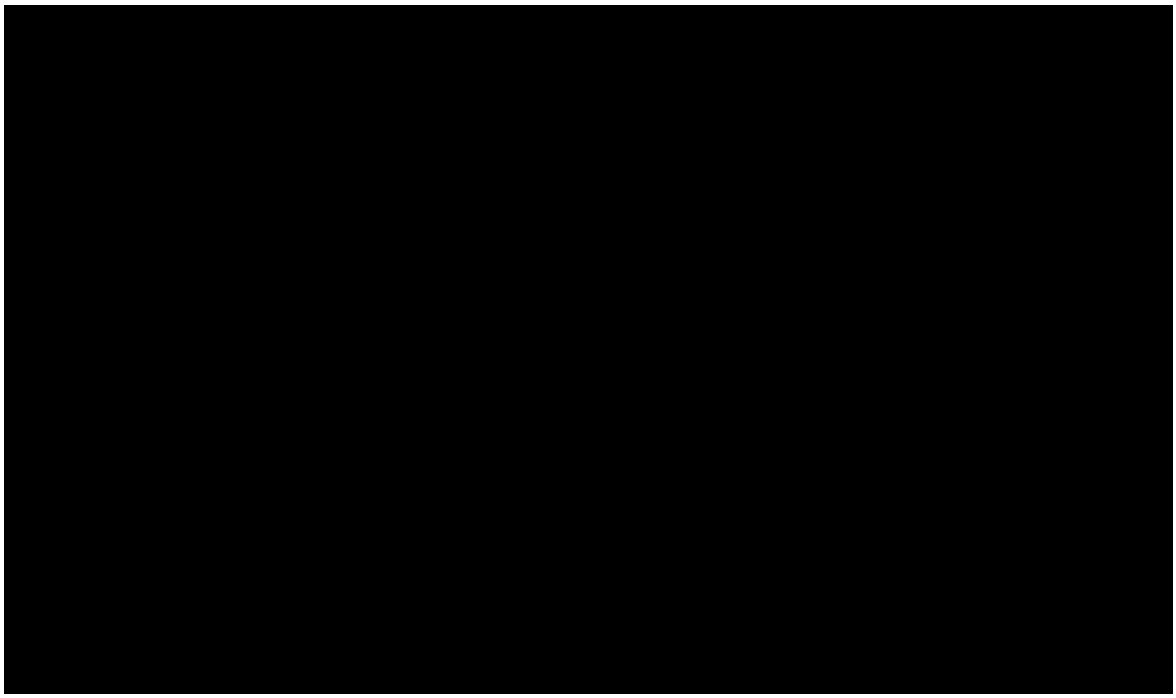
- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in dyspnea symptom score
- Correlation between change from baseline to week 52 in FVC [mL] and change from baseline to week 52 in cough symptom score

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.



10.3 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 summarized in the final study report. Separate tables will be provided for patients with serious adverse events.

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. All analyses will be based on the number of patients with AEs and not on the number of events. 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 (TEAE).

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

Adverse events relating to gastrointestinal perforation and hepatic injury will be considered as adverse event of special interest (AESI) and will be tabulated separately.

11. QUALITY CONTROL

To ensure correct analysis conduct and implementation following Alcedis SOPs will be considered:

- Checklist for FormFake acceptance (SLC03-A09)
- Preparation of Statistical Analysis Plan (SAP) on the basis of protocol and CRF and review (SA02-A02)

- Generation of SAS programs for statistical analyses on the basis of given specifications/SAP (SA03)
- Quality Assurance of SAS programming, code review, cross-output check of SAS programs (SA04-V06)
- Verifying of statistical output, cross-output check (SA04-A01, A03, A07)
- SAS log file provides traceability of the several steps of analysis
- Preparation of the Table, List and Figures (TLFs) (SA05)

12. REFERENCES

12.1 PUBLISHED REFERENCES

[1] *CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.

[2] Trial Statistical Analysis Plan, "A double blind, randomized, placebo-controlled trial evaluating the efficacy and safety of nintedanib over 52 weeks in patients with Progressive Fibrosing Interstitial Lung Disease (PF-ILD)", Boehringer Ingelheim, Study Number c11935728-03, ClinicalTrials.gov

12.2 UNPUBLISHED REFERENCES

None

ANNEX 1. ADDITIONAL INFORMATION

The shell for the tables, figures and listings will be provided as a separate document (TechnicalSAP_1199-0449_v1.0_2022NOV17.docx).

ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

The NIS SEAP must be sent for review to the following individuals **prior to approval**.

Reviewer	NIS involving BI product(s)	NIS not involving BI product(s)	
		Global NIS	Local NIS
NIS Lead	X	X	X
Global TM Epi*	X	X	X
Oversight Data Manager	X	X	X
TSTAT	X	X	X
RWE CoE	X	X	

** When BI NIS lead is not TM Epi*

Study Title: **INREAL – Nintedanib 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**

Study Number: 1199-0449
Protocol Version: INREAL_Protocol_V2 final_08Feb2021.pdf
final version 2.0 as of 8 FEB 2021
Document Number c34369089-02
Local Amendment 1.0 as of 20 JAN 2022

I herewith certify that I agree to the content of the study SEAP and to all documents referenced in the study SEAP.

NIS [redacted]
Name/Date : [redacted] 17.11.2022 | 08:53 CET Signature: DocuSigned by: [redacted]

TM Epi
Name/Date : [redacted] 21.11.2022 | 19:59 CET Signature: DocuSigned by: [redacted]

TDM
Name/Date : [redacted] / 17.11.2022 | 10:32 MEZ Signature: DocuSigned by: [redacted]

TSTAT (BI)
Name/Date : [redacted] 17.11.2022 | 10:16 MEZ Signature: DocuSigned by: [redacted]

TSTAT (CRO)
Name/Date : [redacted] 17.11.2022 | 08:12 MEZ Signature: DocuSigned by: [redacted]

RWE CoE
Name/Date : [redacted] 06.12.2022 | 14:06 CET Signature: DocuSigned by: [redacted]

13. HISTORY TABLE

Table 1: History table

Version	Date	Author	Sections changed	Brief description of change
Draft v0.1	21-JAN-2021	[redacted]	None	This is the first Draft-Version of SEAP without any modification.
Draft v0.2	28-JAN-2021	[redacted]	6.1	Information on study design shortened with reference to the Study Protocol.
			6.3	Inclusion and exclusion criteria deleted and referred to the Study Protocol.
			6.4	Information on study visits shortened with reference to the Study Protocol.
			[redacted]	
			7.3	Covariates referring to patient demographics deleted.
			9.2	Handling of missing values completed: Sections 9.2.1 Change from baseline endpoints and 9.2.2 L-PF added.
			[redacted]	
Draft v0.3	29-JAN-2021	[redacted]	First page	Document Number set to NA.
Draft v0.4	03-FEB-2021	[redacted]	First page	Wording for NIS Data Manager changed to Oversight Data Manager.
				Contact information for Data Manager completed.
			List of abbreviations	RWE CoE, TM Epi, TDM and TSTAT added.
			2	Wording for NIS Data Manager changed to Oversight BI TDM. Data Manager and TSTAT added.
			Annex 2	Wording for NIS Data Manager changed to Oversight Data Manager. Study Number, Protocol Version added.
Draft v0.5	05-FEB-2021	[redacted]	2	Contact information for RWE CoE and TM Epi completed.
			[redacted]	
			12.1	Reference for L-PF changed.
			Annex 2	RWE CoE and TM Epi added.
Final v1.0	26-FEB-2021	[redacted]	First page and Annex 2	TM Epi changed.
Draft v1.1	03-MAR-2022	[redacted]	4	Reason for modification of analysis sets described.
			7	Definition added for Overall survival, Time to premature treatment discontinuation, Time to first dose

Version	Date	Author	Sections changed	Brief description of change
				reduction, Time to first treatment interruption.
			10	Wording for treated set extended with 'signed informed consent'. Per protocol set and important protocol deviations added. Further details added to improve clarity, on which sets analyses will be performed.
Final 2.0	18-MAR-2022	[redacted]	7	Definition modified for Overall survival, Time to premature treatment discontinuation, Time to first dose reduction, Time to first treatment interruption: Start date for the calculation of all time to event analyses was changed from 'signed informed consent' to 'first dose of nintedanib'.
Final 2.1	07-NOV-2022		6.4 10 10.1 ANNEX 2	Time windows for visits were added. Analyses will be done using time windowing. Additionally, sensitivity analyses will be performed for primary and secondary endpoints. No weighting to co-primary endpoints Protocol version changed
Final 3.0	17-NOV-2022		ANNEX 1	Final version of TechnicalSAP added